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AMITOTIC DIVISION IN SENILE TISSUES AS A PROBABLE MEANS OF SELF-PRESERVATION OF CELLS

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In one of our earlier investigations (1) we studied the effects of fatigue on the Purkinje cells of the cerebellum in mice of different ages. In this study we noted that the senile animals, both control and experimental, showed some Purkinje cells which were binucleate. In a later study on alterations of the Golgi apparatus with age in mice (3), binucleate Purkinje cells again were noted in all of the old animals and also a number of cells with the nucleus in the shape of a dumbbell or a horseshoe. Stages in a process of amitotic division of the nucleus were strongly indicated by these figures.

Similar phenomena were observed by Inukai (21) in the cerebellum of albino rats. In animals of 200 days some cells with elongated nuclei and 2 nucleoli were found, and in 3 senile rats of 730, 1017, and 1085 days, the presence of multiple nuclei was noted.

Whether or not the phenomena of amitotic division and binuclearity of the Purkinje cell in old age are found only in rodents has not been settled to our complete satisfaction. There are some indications that the condition is not found as a feature of senility in man (2) although occurring in certain pathologic conditions (4).

In the present investigation the problem of the occurrence of amitosis in the Purkinje cells of old mice has been re-examined. In addition, observations have been made on preparations of human liver tissue.

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SURVEY OF PREVIOUS STUDIES IN AMITOSIS

Mechanism of Amitosis.—According to the classical descriptions of amitosis the nucleolus generally is drawn out at an early stage and then divided into equal parts. Meanwhile the nucleus is elongating into the form of an hour-glass. The nucleus then becomes constricted and divides, generally into equal parts, each with 1 of the 2 new nucleoli. Such a process was called by Flemming (14) amitosis or direct nuclear division, in contrast to the process of mitosis or indirect nuclear division which he described in detail in 1882.

A type of amitosis which is of particular interest is described as "not rare" for many plant cells. The nucleus is divided by the formation of a very delicate fissure without a constriction of any kind and without separation of the 2 daughter nuclei. Later a diaphragm of separation between 2 halves of the nucleus is formed and only then do the 2 daughter nuclei separate. This type of division, seen many times in nature, is the type described as occurring in cells of *Spirogyra* as a result of the action of ether.

Lettré (24) discusses some of the chemical differences which probably determine the basic distinction between amitosis and mitosis. During cell division, as in the cleavage of the sea-urchin egg, the total quantity of nucleic acid is not increased, yet the thymo-

nucleic acid (DNA), present only in small quantity at the beginning of mitosis, increases in amount at the expense of the ribonucleic acid (RNA), so that a formation of DNA from RNA apparently is occurring. This fact is related to the occurrence of amitosis. The nuclear membrane of the resting or interphasic nucleus is a protein membrane upon which are heaped up the nucleic acids or nucleotides. In the separation of the chromatin the nucleic acid is removed from the nuclear membrane, causing it to lose the character of a nucleoproteid membrane and making it, as simply a protein membrane, subject to solution by the action of proteolytic ferments. This, according to Lettré, is the ordinary course of chemical events in mitotic division. If, however, the nucleic acids are not removed from the membrane, it cannot be dissolved. We then obtain the picture of amitotic division.

Occurrence of Amitosis.—Amitotic division accompanied or followed by division of the cell body is not common but yet is not extremely rare if a broad survey of the biologic field is made. Ranvier (30) in 1875 described such division in the lymphocytes of the amphibian, Axolotl, which were observed in a moist chamber. Ranvier even described the observation as simple enough for use as a class exercise. Arnold (7) confirmed his finding.

Clara (10) has described the process of amitotic division in the human liver. His specimens came from a rather heterogeneous group, with the cause of death not known in every case, so that it is difficult to draw conclusions concerning the relationship between age and the occurrence of amitosis from his material. His important conclusion from the study of livers from 20 subjects, however, is that amitosis does occur. He describes and pictures the process of division of the nucleolus in amitosis, a particular observation which seems to us to preclude any contention that he was in reality looking at figures of abnormal mitotic division. As in our own studies, he has found amitosis to be a relatively rare occurrence, but one the reality of which cannot be denied. In an 80 year old person there were 16 constricted nuclei among 5123 cells, while in a 36 year old person there were 15 constricted nuclei out of 3758 cells.

Wassermann (37) also describes amitotic division of the nuclei of liver cells. More recently Schiller (33) has described interesting observations on this phenomenon, again in human liver. He believes that such division serves as a method of freeing nuclei from the large inclusions which often appear in them since one of the daughter nuclei always will lack this "encumbrance."

Rzhevutskaia (32) described what may seem at first consideration to be a very surprising instance of amitosis. He found amitotic division in the spinal ganglion cells of puppies 5 to 7 days old giving rise not only to new nuclei but to new nerve cells. His pictures seem very convincing. The new cells are at least at first contained within the same capsule and may show perfectly parallel, flattened edges of the cell bodies.

Observations on living cells in tissue cultures have yielded some data on the occurrence of amitotic division. Holmes (20) saw amitotic division of the nuclei in ectodermal cells of the adult frog without cytoplasmic division. Kreibich (22) described amitosis of epithelial cells of the epidermis and cornea of the pig. Lewis and Webster (26), after prolonged watching, observed a single case of direct cleavage of the nucleus without division of the cytoplasm in an epithelioid giant cell. They believed, however, that amitosis is the regular manner of formation of multinucleate giant cells in cultures of lymph nodes, and found all stages of amitosis in them. In embryonic chick liver grown in vitro Lynch (27) observed direct division of the nucleus without cell division.

In general, observations of amitosis in living cells are rather rare, and Lewis and Lewis (25) reported that they had never seen amitosis in cultures of embryonic chick material. Nevertheless, they stated (p. 146): "There are so many indications of the pro-

cess, however, especially in older cultures, that it is hard to believe it does not occur more frequently than the observations on living cells would indicate." Various stages of fragmentation and budding of nuclei also occur in many older cultures. Cells with such nuclei often are degenerate, as evidenced by extensive vacuolation, granular rather than filamentous mitochondria, and a reduction in the total mitochondrial content.

Cowdry (11), in a study of the mitochondria during cell division in chick embryos (fixed material) reported 907 of the cells studied as being in mitosis, 93 in apparent amitosis.

In the field of tissue culture studies, Bucher (9) described amitosis as a rare occurrence in normal cultures of fibroblasts but readily observed in cultures which were fixed 48 hours after the end of the action of colchicine upon them. In such amitoses, he said, there is no trace of formation of chromosomes, while the nuclear membrane and the nucleoli, except for division of the latter, remain absolutely intact. There is therefore no possible confusion with pseudoamitosis, a confusion against which Politzer (29) has cautioned.

In both the older and more recent literature, then, descriptions of amitotic division in a variety of cells are not lacking.

Significance of Amitosis.—It was observed by Nathansohn (28) that cells of *Spirogyra* which had undergone amitosis as a result of the action of ether were capable of ordinary mitosis when filaments were placed in water. This fact tends to discount the "sentence of death" which some cytologists have sought to pronounce on all cells undergoing amitosis. Häcker (15) similarly found that the cells of embryo cephalopods which had undergone amitosis could again resume mitotic division.

Amitosis has been described as the common method of reproduction in some cells which hardly can be considered degenerate. Thus Regaud (31) has described this as the mode of division of the cells of Sertoli in the testis.

It is true, however, that amitotic division of nuclei seems to be less often concerned with multiplication of cells than with the reproduction of nuclei within an individual cell to increase the nuclear surface and thus aid in metabolic activity when "excessive" growth has occurred or when unfavorable conditions threaten the life of the cell. Dogiel (12) described it as occurring among the cells of the superficial layers in the epithelium of the urinary bladder. Such a process apparently occurs in the formation of some types of giant cells, in the follicle cells of eggs both among invertebrates and vertebrates, and in the embryo sac of phanerogamic plants. Other important instances of amitosis are in the division of nuclei in developing skeletal muscle when fibrillae are beginning to be formed and in the syncytial tissue of the placenta (18).

The amitotic process generally occurs in cells with large nuclei. Bucher (9) believes that it is caused not by the direct action of colchicine but through a modification of the internal organization of the nucleus (probably polyploidization) and that the process through the production of 2 or 3 nuclei in a cell restores the proper ratio between nuclear surface area and volume required for the metabolism of the cell.

Our citation of a number of the earlier authors does not mean that we believe that their conclusions should be accepted without considering the very real possibilities of misinterpretation. In view of more recent studies, however, including our own findings in senile tissues, we believe that these earlier descriptions should not be cursorily dismissed as obviously in error.

Present Studies

Material and Methods

For the present investigation we have gone back to the study of the cerebellum of the mouse, the type of material in which our first observations on amitotic division were made. We have attempted, first, to ascertain the general picture of this process in re-

gard to the frequency of its occurrence in animals of different ages. Second, we have attempted to study carefully the individual stages in the process to see whether it occurs in a perfectly constant manner, or if variations occur, what they may be. Third, we have given attention to the manner, if any, in which the cytoplasmic body, with its distinctive form in the Purkinje cells, may be affected by the nuclear division.

As a subsidiary to the study of the nerve cells in the senile mouse, we have initiated observations on the brains of starved animals, in which we thought that the tendency to amitosis might be increased. While this phase of the work is in an initial stage, chiefly because of the lack of more senile animals, we present some data from the study to date.

Lastly, as a cell type for comparison, we have examined the liver of a number of human subjects to see if we could confirm earlier reports of amitotic division in the hepatic cell.

The mice used in our study of the Purkinje cells comprise 12 animals of the C57 Black strain. The ages ranged from 4 to 6 weeks up to 23 to 25 months (table 1). The mice had been kept for some weeks in clean plastic cages in our own animal room after reaching us from the Jackson Memorial Laboratory. They were fed on Purina dog chow, containing all of the essential nutritional factors, and had ample supplies of water.

The ages of 4 of the mice, 2 of the 11 to 12 weeks and 2 of the 23 to 25 months, made them well-paired for an examination of the possible effect of starvation on the frequency of occurrence of the binucleate condition. Although the number of older animals was small, it was considered worth while to employ one of them in this way since our earlier

TABLE 1. DATA ON THE CEREBELLA OF C57 BLACK MICE AT DIFFERENT AGES, BASED ON THE STUDY OF 1000 PURKINJE CELLS IN EACH ANIMAL.

Age and Sex	Binucleate Cells	Cells with Nuclei of Altered Form	Cells with Nuclei of Normal Form but with 2 Nucleoli	Cells with Aberrant Shape of Cell Body
4-6 week Female	0	3	3	0
11-12 week Female Fed	1	5	0	0
11-12 week Female Starved	2	9	4	0
6-10 month Male	1	9	0	2
6-10 month Male	3	11	0	1
6-10 month Male	5	8	0	2
18-20 month Female	4	6	2	1
18-20 month Female	0	5	2	5
18-20 month Female	6	4	2	2
18-20 month Female	6	8	1	0
23-25 month Female Fed	20	32	0	3
23-25 month Female Starv'd	40	32	2	9

work (3) already had shown that binucleate cells are increased in number in old age.

Ten of the animals, therefore, were sacrificed while in a normal, well-fed condition. Two of the animals, 1 of the 11 to 12 week ones, and 1 of the senile, 23 to 25 month ones, were starved for one week, having sufficient water but no food during this time, and then sacrificed.

The brains of all animals were divided into right and left halves. The right halves were used in making Nissl preparations, the left in special preparations such as the DaFano silver impregnation for cell form and Golgi apparatus or the Altmann's acid aniline fuchsin method for mitochondria with Regaud fixation. The present report is chiefly on the Nissl preparations. The half of the brain used for this purpose was fixed in alcohol, cleared in xylol, infiltrated and embedded in paraffin, sectioned sagittally at 4 μ, and stained with cresyl violet.

The method used in studying amitotic phenomena was to follow the border of the granular layer of the cerebellum until observation on 1000 Purkinje cells in each animal had been made.

The studies on human liver were carried out on 10 autopsy specimens from subjects with varied causes of death. The object here was not a quantitative study but an exploration of the tissue for figures of amitotic division. The subjects studied are listed in table 2.

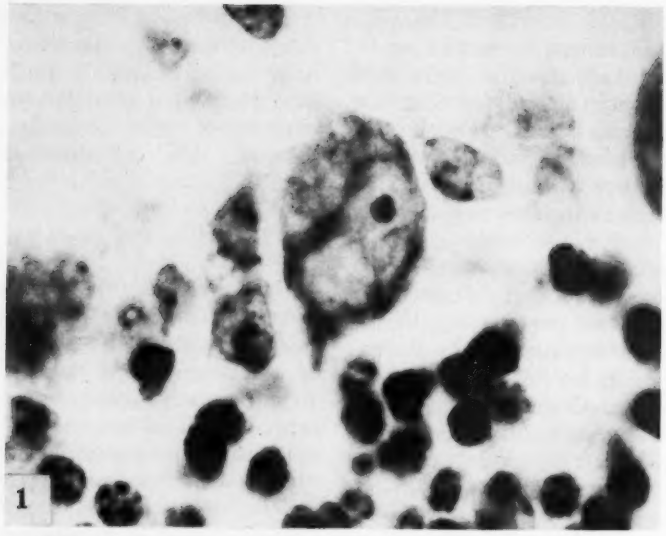
Observations

Cerebellum of Mice.—A study of table 1 shows that binucleate Purkinje cells seem to be present, although in very small numbers, at a relatively early age. While none was found in the youngest mouse, the 11 to 12 week control animal showed 1 out of 1000 cells, the starved animal only 2. The 6 to 10 month animals, representing a somewhat heterogeneous group in relation to age, showed from 1 to 5 binucleate cells each.

In the 18 to 20 month old animals, the number of binucleate cells observed per thousand varied from 0 to 6. In the senile animals the normally fed mouse showed 20, the starved one 40 such cells. A Purkinje cell in the process of amitotic division is presented in figure 1.

Table 2. Autopsy Subjects Used in a Study of Amitosis in the Human Liver.

Age and Sex	Race	Cause of Death
50 year Female	Negro	Pulmonary embolism
55 year Male	Negro	Acute congestive heart failure, pulmonary tuberculosis
64 year Female	Negro	Metastatic hypernephroma of right kidney
67 year Male	White	Cerebellar herniation
70 year Female	White	Purulent bronchitis
71 year Female	White	Thrombosis, left internal capsule
72 year Female	White	Coronary thrombosis
80 year Male	Negro	Peritonitis, pulmonary infarction, pneumonia
81 year Male	Negro	Uremia, fever of central nervous etiology
96 year Male	White	Acute cardiac failure, coronary occlusion



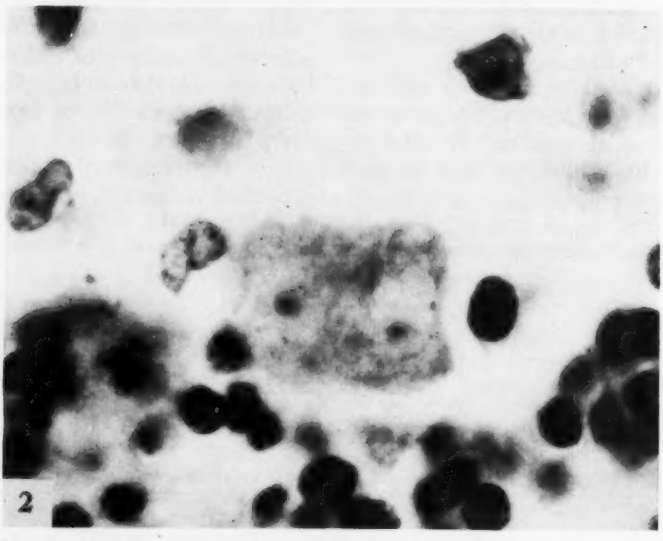


FIG. 1. Purkinje cell in the cerebellum of a 702 day old mouse. The nucleus is constricted in the process of amitotic division. Cresyl violet. X1822.

FIG. 2. Large, binucleate Purkinje cell in the cerebellum of the same animal. Each nucleus contains a prominent nucleolus. The voluminous cytoplasm is so disposed as to give a form to the cell which is very unusual for this particular cell type. Cresyl violet. X1822.

The appearance of the binucleate cells was not the same in every instance nor in every animal. The usual arrangement, and that seen almost without exception in the binucleate cells in the senile animals, was the presence of 1 nucleus at each side of the cell body, as shown in figure 2. Another arrangement was that in which there was 1 nucleus in its normal position and another, generally smaller nucleus between it and the portion of the cell body from which the apical dendrite arises. This latter condition was true in 6 out of the 9 binucleate cells found in the 6 to 10 month animals, but seldom seen in the senile mice.

Generally a nucleolus could be found in both nuclei and very frequently a nucleolus was seen in each half of a constricted nucleus as though the division of this body were complete before the nuclear division. In some cases, however, we were unable to see any nucleolus in 1 nucleus, even in studying serial sections. Such seemed to be particularly the case with the apical nuclei of the 6 to 10 month mice which we have mentioned.

The cells with nuclei of altered form represented chiefly constricted or lobed nuclei. It was not always possible to say whether such nuclei indicate a process of amitotic division, although in many instances such a process seemed strongly indicated or practically certain (fig. 1).

It was interesting to note that constriction and lobation did not seem to be the only method by which a nucleus may form 2 daughter nuclei even within the rather homogeneous type of the Purkinje cells. In a number of instances a delicate line of division, a split or furrow, seemed to divide the parent nucleus without its changing shape. It will be recalled from our survey of previous studies in amitosis that this type of division has been described in plant cells, and Bucher (9) has observed it in fibroblasts. We have seen it also in the salivary glands of senile rats (5, 6) and in the lesions of senile keratosis.

We were interested in the third item in table 1, namely, the number of cells with nuclei of normal form but showing 2 nucleoli, because we wished to know whether there was evidence of a prior division of the nucleolus before the nuclear form was altered. In other parts of the nervous system in rodents and some other animals, as in the spinal ganglia, the presence of 2 or more nucleoli in a nucleus is not uncommon. In the Purkinje cells, however, as our table shows, this is an unusual condition, with only 16 out of the 12,000 cells showing 2 nucleoli in the same section. There seemed to be no relation between this condition and age nor between it and the number of cells with 2 nuclei or in process of amitotic division.

The last item in table 1 is one concerning the shape of the cell body and involves the question to what extent the cytoplasm may share in the division process. A number of cells with 2 nuclei were obviously of greatly increased transverse diameter (fig. 2). Some of these depart widely from the classical somewhat pear-shaped picture of the Purkinje cell. In classifying cells as having an aberrant shape of the cell body we have tried to list only those which are conspicuously aberrant, and the numbers given were not large. Some individual cases, however, were so suggestive of a tendency of the two portions of the cell to separate from each other, particularly in our senile starved animal, that we examined carefully a number of slides prepared by silver impregnation (Da Fano) which delineates the cell shape better than do the Nissl preparations. We present figure 3 as an example which has been rather convincing to us of the possibility of cytoplasmic division occurring and continuing through the cell body and into the basal axon, leaving 2 "cells" attached to a common axon which is of a Y-shape. As to the functional capacity of such a morphologic arrangement, we would find it difficult to comment.

Human Liver.—The survey of liver tissue from 10 human autopsy subjects has yielded figures which we believe definitely are amitotic. These figures are not numerous and thousands of cells often must be ex-

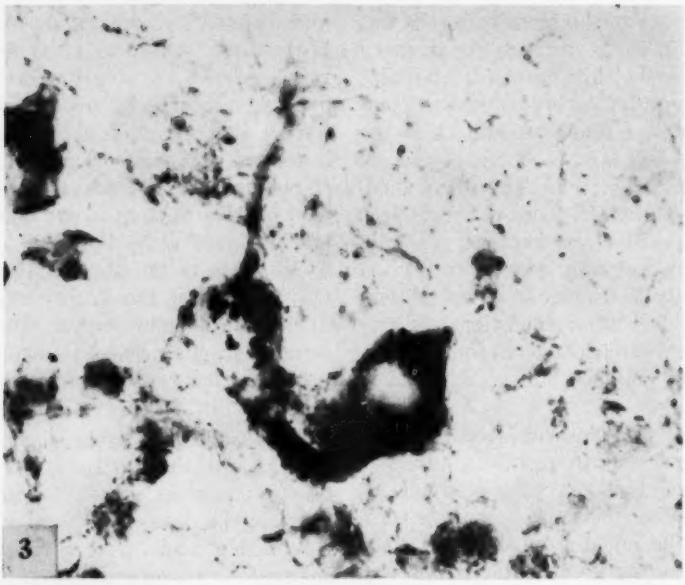
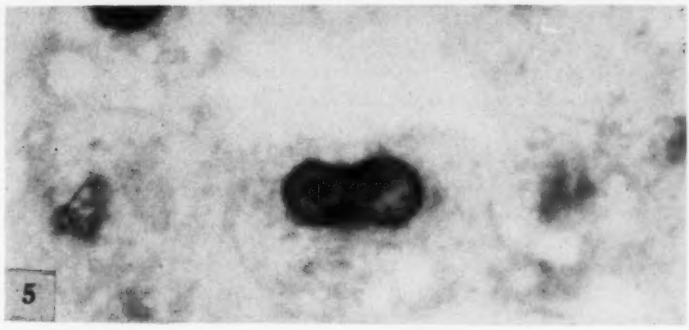
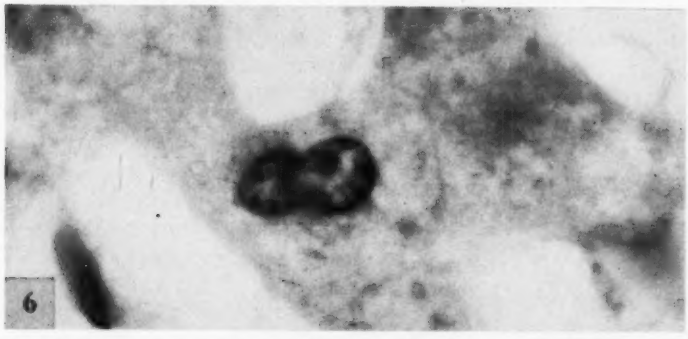
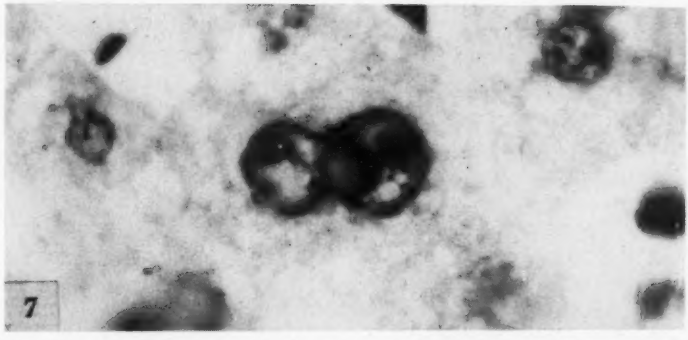


FIG. 3. Apparently "double" Purkinje cell in the cerebellum of a senile mouse which had been deprived of food for several days. The cell seems to have undergone a fission extending through its body and a short way along the axon. Da Fano silver preparation X1522.

FIG. 4. Cell from a spinal ganglion of a senile dog, 12 years of age. The very large vacuole on the left represents a stage in fatty degeneration. The binucleolate condition is not uncommon in ganglion cells, but this degenerate cell seems to show a tendency to duality of the nucleus itself. Preparation courtesy of Dr. N. Sulkin. Cresyl violet. X1822.







FIGS. 5-7 are from the liver of a 72 year old white woman, who died of coronary thrombosis. There was a history of diabetes mellitus in this subject.

FIG. 5. Amitotic division of a small nucleus in the liver. The 2 daughter nuclei here will be approximately equal in size and each contains a nucleolus. X1822.

FIG. 6. Amitotic division of a small nucleus, in which the resulting nuclei apparently will be of somewhat unequal size. X1822.

FIG. 7. Amitotic division of a large nucleus in the liver. This nucleus contains one of the inclusion bodies common in senile livers and this body occupies a portion of the constriction. X1822.

amined to yield one. With the heterogeneous features of the subjects studied, we would not be able to relate these figures closely to the age of the individual but the fact of the real occurrence of this process we believe can hardly be doubted (figs. 5, 6, and 7). It is hoped that studies on laboratory animal material may help to relate the occurrence of amitosis in the liver in a more definite way to the aging process, as has been done for nervous and for other glandular tissues in such animals.

Discussion

Our studies on senile tissues, including particularly gland cells (submandibular and parotid glands) and nerve cells, show that the process of amitosis occurs in such tissues, not in a large number of cells but in a consistent manner not seen in the same tissues in younger animals. The result of the amitotic division of the nucleus probably is for the most part the creation of binucleate cells which are better able to survive under the conditions prevailing in the senile tissues.

In the nervous system, a definite tendency to degeneration and death of individual cells has been shown to occur in old age.

Hodge (19) found a 25 per cent loss of Purkinje cells in a man of 92 years as contrasted with one of 47 years. Harms (17) found 16 Purkinje cells in a senile ape (*Pithecus fascicularis*) for every 41 such cells in a young ape of the same species. In an 80 year old woman this author found 5 or 6 Purkinje cells, of which only 2 were apparently functional, for every 20 in a young person.

Ellis (13) gave figures on numbers of Purkinje cells in a given area of cerebellum as follows: 823 in a man 42 years old; 591 in a man 65; 500 in a man 79; 462 in a man 94; and 445 in a man 100.

In the dog Harms (16) found 31 Purkinje cells in a 2 year old animal; 20 in a 14 year old one; and 10 in one 17 years old, in comparable areas.

In the rodents, Spiegel (34) found the loss of Purkinje cells in senile guinea-pigs to be as high as 40 per cent. The degeneration of the cells, according to him, takes place in serial fashion, involving as many as 20 to 25 cells in a row on a given section. Inukai (21) found the number of Purkinje cells in the rat at over 1000 days to be 79.6 per cent of that at 200 days and in the male, 81.6 per cent. Our own findings on the cerebellum of the mouse show a comparable degree of loss of cells in this species in senility.

Truex (35) has shown that fatty degeneration of individual cells in sensory ganglia in man is responsible for the loss of many neurons after middle age. Truex and Zwemer (36) studied this process in the Gasserian ganglion and in spinal ganglia in old cats and rats and found it to be widespread in this animal material also.

Studies on parts of the nervous system other than the cerebellum and sensory ganglia show evidence of cell loss both by counts on cells (Brody on the cerebral cortex, 8) and by degenerative changes seen in them (Kuntz, on the autonomic ganglia, 23). An illustration of a binucleolate spinal ganglion cell with fatty degeneration from a senile dog is presented in figure 4.

It therefore seems clear that in the nervous system of the senile animal or man we are dealing with a population of cells which shows a rather high mortality and in which probably many or all of the cells are having to combat unfavorable conditions of existence. Under such conditions the process of amitotic division may be a not unimportant one in preserving cells which otherwise would be totally lost to the organism.

The question as to whether amitotic division ever results in the formation of new cells in senile tissues is difficult to answer. In the nervous system, where such a happening might seem least likely to occur because of the highly differentiated nature of the cells, we find some definite changes in form of the cell body in cases where 2 nuclei have been formed by amitosis and in rare instances (fig. 3) the cytoplasm seems to share in the division.

It is hoped that further studies using the silver methods for delineation of cell form

may add to our knowledge of the potentialities of amitotic division.

Summary

Observations on the tissues of senile animals give evidence of an occurrence of true amitotic division, particularly in the salivary glands and in portions of the nervous system.

A re-examination of the amitotic process as it occurs in the Purkinje cells has shown differences in detail as to the way in which the nucleus may divide. A participation of the cytoplasm in the division in some cases is strongly suggested by the present study.

Survey of autopsy sections of human liver yields figures of amitotic division of nuclei.

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WIDTH AND LENGTH OF COLLAGEN FIBRILS DURING THE DEVELOPMENT OF HUMAN SKIN, IN GRANULATION TISSUE AND IN THE SKIN OF ADULT ANIMALS*

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THE width of collagen fibrils has been studied with the electron microscope by Gross (2), von Pahlke (4, 7), and Schwarz (6, 7). They found that the average width of the fibrils increased with age. This change had ceased by 60 days in the rat skin (Gross), by 7 to 8 months of fetal development in human sclera (Schwarz), by 4 years in the femur (Schwarz and von Pahlke), and by at least 13 years in human Achilles tendon (von Pahlke). When the human cornea was examined, however, the fibrils remained in their narrow fetal state regardless of age (6). In tissue cultures of fibroblasts, Porter and Vanamee (5) also observed an increase in collagen fibril width with increasing age of the culture.

A comparison of the number of natural (tapered) ends in a preparation of collagen with the number of broken ends gives an indication of the length of the collagen fibrils. A high percentage of tapered ends in a sample indicates that the majority of the fibrils are shorter than in a sample with a low percentage of tapered ends. Banfield (1), from general observations of mesenchymal neoplasms and human adult and embryonic skin, found that collagen fibrils with tapered ends occurred with greater frequency where collagen was apparently being actively formed. Keech (3) in an extensive survey of newborn and adult human skin found that the percentage of tapered ends did not exceed 11.2 per cent. The present paper will extend the above observations to include embryonic human skin, the skins of a variety of adult animals, and two samples of granulation tissue.

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MATERIAL AND METHODS

Formalin fixed abdominal skin from human fetuses measuring 6.8 to 18 cm. crown rump and a limb bud of a 2.5 cm. embryo was macerated in distilled water with a Waring blendor. Preparations for the electron microscope were made from this material and shadowed with palladium. Because of the difficulty of obtaining sufficient abdominal skin the entire limb bud from the 2.5 cm. embryo was used.

Similar preparations were made from the abdominal skin of a 1095 Gm. (7 month) fetus, a 3 year old child, and 3 adults 65, 68, and 85 years of age.

Samples of granulation tissue were obtained both from a case of chronic osteomyelitis, and from a case of lupus erythematosis disseminatus with pericarditis. Samples of pericardium thickened with dense collagen from the latter case were also examined.

Abdominal skin of adult rabbits, guinea pigs, rats, hamsters, and gray and white mice was used.

For most of the specimens, 200 or more fibrils were photographed at approximately 4800 times magnification. Their widths were measured on a screen from a delineascope projection to a final diameter of approximately 86,000 times. Histograms were constructed for each sample, and the mean and standard deviation of the mean width were computed for each sample.

The proportion of tapered ends of the collagen fibrils was obtained by counting 200

or more ends and computing the percentage of tapered to total ends.

RESULTS

Human Abdominal Skin.—Figure 1 is a

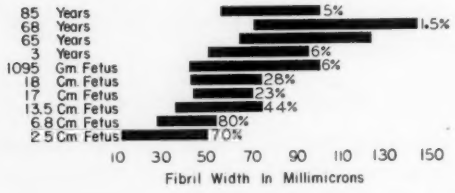

FIG. 1. Human abdominal skin. Bars represent the mean width plus and minus twice the standard deviation of the mean width of collagen fibrils from specimens of human abdominal skin of different ages. The figures to the right of the bars indicate the percentage of collagen fibrils with tapered ends in each specimen.

bar graph of the mean and twice the standard deviation of the mean width of the collagen fibrils from the skin of embryo, fetal, premature, and adult humans. The figures from which the graph was made are presented in table 1. There is an increase in width from the 2.5 cm. embryo to the adult. In the electron photomicrographs, figure 2, the marked

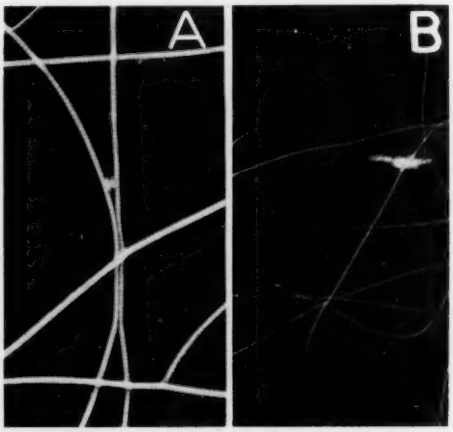

FIG. 2. Collagen fibrils from human abdominal skin.
(A) 65 year old adult. 10,560 X.
(B) 6.8 cm. fetus. Note numerous tapered ends. 10,560 X.

difference in fibril width between a 6.8 cm. fetus and a 65 year old adult is clearly seen. The spread of fibril widths is greater in the 1095 Gm. fetus and the adults than in the smaller fetuses where the widths are amazingly uniform. This, however, was not true in the case of one 6.8 cm. fetus which was excluded from table 1 and figure 1. Here broader fibrils were found as indicated by the histogram figure 3. This may be the result

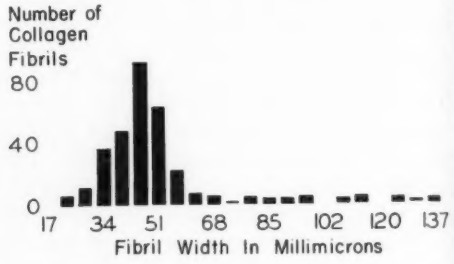

FIG. 3. Histogram of collagen fibrils from abdominal skin of a 6.8 cm. embryo. The height of the bars represents the number of collagen fibrils. Widths are indicated below.

of contamination with some tissue other than skin. Representative histograms from another 6.8 cm. fetus, an 18 cm. fetus, and an adult are shown in figure 4. Here again the greater spread in widths of the adult is demonstrated. In the adults the very narrow fibrils are not found. In the 1095 Gm. fetus one fibril 22.8 $\mu\mu$ wide and one fibril 34.2 $\mu\mu$ wide were found in 325 fibrils measured. In general, however, the width of the narrowest fibrils increased with increasing age.

The numbers beside the bars in figure 1 represent the percentage of tapered fibril ends in each specimen: 70 per cent in the 2.5 cm. embryo; 28 per cent in the 18 cm. fetus; and 6 per cent in the 1095 Gm. fetus. The percentage of tapered ends for the older age groups was not significantly different from that of the 1095 Gm. fetus.

Human Granulation Tissue.—A photomicrograph of the granulation tissue from the chronic osteomyelitis is seen in figure 5. All the collagen bundles were quite narrow.

TABLE 1. MEAN WIDTHS WITH STANDARD DEVIATION OF COLLAGEN FIBRILS FROM ABDOMINAL SKIN, GRANULATION TISSUE AND DENSE COLLAGENOUS THICKENING OF PERICARDIUM.

Species	Electron Microsc. Number	Weight (Gm.)	Length (Cm.)	Width and Standard Deviation ($\mu\mu$)	% Tapered Fibrils
		Crown Rump Measureme't (Cm.)			
Human Fetuses	534	2.5		31.0 ± 9.2	70
	532	6.8			47
	533	6.8		41.4 ± 6.6	80
	531	13.5		55.8 ± 9.2	44
	545	17.0		57.4 ± 6.5	23
	541	18.0		58.5 ± 7.8	28
		Weight (Gm.)			
	522	1095		71.2 ± 14.8	6
		Age Years			
Human	582	85		78.5 ± 10.6	5
	520	68		107.0 ± 17.8	1.5
	521	65		94.0 ± 14.5	
	583	3		73.5 ± 11.0	6
Granulation Tissue		Chronic osteomyelitis		36.4 ± 5.8	32
		Lupus pericarditis		59.0 ± 12.2	10
Thickened Pericardium (Lupus)				93.0 ± 15.5	6
Rabbits	540	2380	45	82.4 ± 14.9	8.0
	547	2900	44	79.5 ± 14.8	8.5
	548	2880	44	75.8 ± 9.2	6.5
Guinea Pigs	538	640	24	96.0 ± 18.1	9.0
	543	635	30	77.7 ± 14.2	7.0
	544	795	30	77.5 ± 12.9	3.0
	556	590	25	83.6 ± 17.4	
Rats	536	140	14	77.5 ± 12.5	13.0
	564	277	22	69.0 ± 11.3	7.0
	565	315	21	78.0 ± 10.0	
	567	525		78.0 ± 12.6	13.5
Hamsters	539	113	12	69.0 ± 11.8	7
	549	95	12	74.2 ± 8.9	6
	550	147	14	72.6 ± 11.8	9
Mice, Gray	535	16	7	63.0 ± 12.5	4.5
	537	16	7	72.5 ± 15.0	7.0
	537	16	7	81.4 ± 12.4	6.0
Mice, White	554	31	10	76.5 ± 13.0	26
	555	33	9.5		7
	579	25	8.5		3

Laidlaw's silver stain showed roughly 90 per cent collagen staining brown and 10 per cent reticulum staining black. The mean fibril width was 36.4 ± 5.8 μμ which corresponded to that of a young embryo. The fibrils were

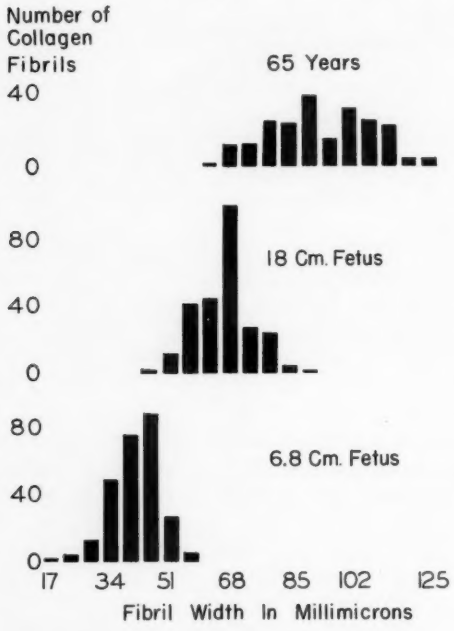

FIG. 4. Histograms of collagen fibrils from human abdominal skin of a 65 year old woman, an 18 cm. fetus, and a 6.8 cm. fetus. Height of bars represent the number of collagen fibrils. Widths are indicated below.

also correspondingly short with 32 per cent tapered ends. In the case of the pericarditis, the granulation tissue had a mean fibril width of 59.0 ± 12.2 μμ, which was narrower than any adult skin. However, the thickened pericardium from the same case which was made up of dense collagen had a mean fibril width which was well within the adult range. These figures are presented in table 1. Tapered fibrils represented only 10 per cent of the total in the pericardial granulation tissue and 6 per cent in the dense collagenous thickening of the pericardium.

Animal Abdominal Skin.—The data for widths and percentage of tapered ends in

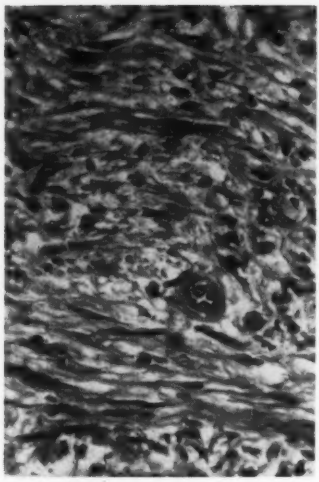

FIG. 5. Granulation tissue. Note the cellularity of the tissue and the narrow width and fibrillar nature of the collagen bundles. 900 X.

preparations of collagen fibrils from animals of various species are presented in table 1. The widths of the fibrils were similar for all the animals regardless of species. The percentage of tapered fibrils did not exceed 1 per cent except in one instance of the white mouse where 25 per cent was recorded.

DISCUSSION

The present study, as well as those of Gross (2), Porter and Vanamee (5), von Pahlke (4, 7), and Schwarz (6, 7), indicates that the general width of the collagen fibrils increases with age. In human skin there is more variation in fibril width in the more mature sources of collagen than in fetal sources below 7 months. The increased variation in width in the mature sources was also apparent in human Achilles tendon and sclera (4, 6).

In the granulation tissue from the chronic osteomyelitis the fibrils were identical in width and length with those of the young embryo. In the granulation tissue from the pericardium the widths corresponded to those of a 17 cm. fetus. It would seem, then, that narrow fibrils (30.0 to 55.0 μμ) and fibrils with a high percentage of tapered ends

(generally greater than 20 per cent) are common to newly formed collagen both in natural development and in the repair process. Conversely, collagen fibrils from dense scar tissue and the denser collagenous dermis in the adult skin are wider and longer than from sites where the fibrils are known to have been more recently formed.

From table 1 it would seem that since the percentage of tapered ends in the 1095 Gm. fetus is no greater than that found in older specimens, the increase in length of the collagen fibrils ceases by the 7th month of fetal development. This, however, cannot be inferred since the method may not be able to differentiate between fibrils of different length once a certain length is reached. The increase in fibril width seems to have stopped at about 7 months of fetal development. This corresponds to the observation of Schwarz (6) on human sclera.

Fibrils narrower than 57.0 $\mu\mu$ were not seen in the adult specimens. It may be, however, that the narrower fibrils are present in the older specimens but are so overshadowed by the number of wider fibrils that a much greater sampling would be necessary to find them.

Species including large and small animals were selected to find out whether the size of the animal determined the size of the collagen fibril. The animals themselves were not selected but taken at random. The only prerequisite was that they be adults. There was no significant difference between widths of the collagen fibrils from the skin of the various animal species. The percentage of tapered fibrils was similar for all species except for the instance of one white mouse which registered 26 per cent. Two other white mice, however, gave only 3 and 7 per cent tapered ends so that this one high figure cannot be adequately explained.

Although the gray mice were approximately the same size as the 6.8 cm. fetus, the mean widths of the collagen fibrils of the mice were 63.0 to 81.4 $\mu\mu$ whereas that of the fetus was 41.4 $\mu\mu$. The mice had from 3.5 to 6 per cent tapered fibril ends compared to 47 and 80 per cent in the 6.8 cm. fetuses. It is, therefore, the immaturity rather than the size of the animal which is responsible for a high percentage of narrow tapered fibrils in the skin.

Summary

A determination was made of the widths and the comparative length of collagen fibrils from the skin of fetal and adult humans, granulation tissue, dense scar tissue, and the skin of adult animals. During the fetal development there was an increase in the widths of the collagen fibrils in the human skin and a corresponding increase in the comparative lengths. Young granulation tissue contained a high proportion of narrow tapered fibrils while the dense scar tissue contained a high proportion of wide fibrils with a low incidence of tapering. There was virtually no difference in widths and percentages of tapered fibrils from the skins of adult humans, rabbits, guinea pigs, rats, hamsters, and mice. The immaturity and not the size of the animal is responsible for a high percentage of narrow tapered fibrils in the skin.

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DEHYDROGENASE ACTIVITIES OF HUMAN AORTIC TISSUE DETERMINED WITH THE TRIPHENYL TETRAZOLIUM TECHNIQUE*

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THE reduction of tetrazolium salts by tissue preparations permits an evaluation of the activities of the dehydrogenating enzyme systems. Procedures have been developed with triphenyl tetrazolium chloride by Kun and Abood (7), Black and Kleiner (1), and Black, Zweifach, and Speer (3), in which the reduced tetrazolium (formazan) formed by the enzyme action is extracted from the tissue and its quantity determined photometrically, thus affording a measure of the metabolic activity. By comparison of the magnitude of the formazan formation by the tissue in the presence of various substrates information is obtained with regard to the relative activities of different dehydrogenases.

In the present study the quantitative tetrazolium technique has been applied to intact samples of human aortic tissue (intima-media preparations). In the choice of substrates particular attention has been given to intermediates of the Krebs' tricarboxylic acid cycle.

METHODS

Thirty-five samples of human aortas were obtained fresh at autopsy at the St. Louis City Morgue.† The age of the individuals from whom the samples were obtained ranged between 4 months and 85 years. The thoracic aorta was removed with sterile instruments. The severed closed segment of the vessel was immediately placed in a sterile beaker immersed in crushed ice. For the tissue metabolism determinations the adventitia was stripped off, and circular segments of the aorta, consisting of the intima and media, were cut out and weighed. The average weight of each segment was 680 mg.

In the report of the experimental procedure used the quantitative tetrazolium technique employed will be described in detail, since it has been possible to improve the method in various respects.

TECHNIQUE FOR DETERMINATION OF TETRAZOLIUM REDUCTION

Reagents:

1 per cent solution of triphenyl tetrazolium chloride in water. The tetrazolium preparation obtained from Pannone Chemical Co., Verona, N. J., was found satisfactory. The triphenyl tetrazolium solution was prepared fresh before use.

0.5 M substrate solution. The substrates used included glucose, lactate, acetate, pyruvate, citrate, iso-citrate, cis-aconitate, alpha-ketoglutarate, succinate, fumarate, l-malate, and oxalacetate. The pH of the substrate solutions was adjusted to 7.1.

Modified Krebs' phosphate buffer, pH 7.1. The composition of the buffer was the same as described in a previous publication (5), except that no glucose was added.

Acetone, reagent quality.

Procedure:

A set of test tubes, measuring 20 x 150 mm., was employed for each experiment. The comparatively large size of the tubes was chosen to reduce the areas of contact between the tissue samples and the sides of the tubes.

In the experiments with substrate solutions 1.5 ml. of buffer, 1.5 ml. of substrate solution, and 2.0 ml. of triphenyl tetrazolium chloride solution were measured into each tube. The tube for determination of the tetrazolium reduction in the absence of added substrate contained 3.0 ml. of buffer and 2.0 ml. of tetrazolium solution. After mixing of the contents the tubes were placed in a water bath at 39 C. and

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† The authors are indebted to Dr. J. J. Connor for assistance in obtaining specimens.

preheated for fifteen minutes before the addition of the tissue samples.

The segments of aortic tissue were rinsed free of adhering blood with successive small portions of buffer solution. The samples were then placed in the preheated solutions and allowed to remain in the water bath for exactly forty minutes. At the end of this period the tubes were removed from the bath and the solutions poured off. The tissue samples were then rinsed rapidly in the tubes with two sets of 5 to 10 ml. of distilled water and the water discarded.

For extraction of the formazan from the tissue approximately 4.5 ml. of acetone was immediately added to each tissue sample and left in contact with the tissue for fifteen minutes. During this time the tubes were shaken three or four times. At the end of the fifteen minute period the acetone was decanted into another tube, graduated at 10.0 ml. volume. A second portion of 4.5 ml. of acetone was then added to the tissue, and after fifteen minutes similarly transferred to the graduated test tube. During this second extraction period the tubes were shaken twice. The combined acetone extract was finally made up to 10.0 ml. volume, and, after mixing, filtered through a Whatman No. 2 filter paper (9 cm. diameter). The color intensity of the filtrate was read against acetone in a Coleman No. 14 spectrophotometer at a wave length of 470 $\mu\mu$.

A tissue blank was run with each set of analyses. This blank furnished a correction for tissue pigments extractable with acetone. Five ml. of buffer solution (without addition of triphenyl tetrazolium) was preheated in the water bath for fifteen minutes, after which the tissue sample was added and left in the bath for forty minutes. The subsequent treatment of the sample was similar to that of the other samples. The average optical density of the blank at 470 $\mu\mu$ per 1 Gm. of wet tissue valued 9 per cent of that of the sample in succinate medium.

A blank on the reagents performed without the addition of tissue consistently gave a zero reading.

For construction of a standard curve a 0.01 per cent solution of triphenyl tetrazolium chloride was prepared. Two-tenths, 0.4, 0.6, 0.8, and 1.0 ml. of the solution was pipetted into test tubes and the volumes adjusted to 1.0 ml. with distilled water. A tube containing 1.0 ml. of water served as a blank. One-half ml. of a freshly prepared 20 per cent aqueous solution of sodium hydrosulfite was then added to each tube and the contents were mixed. The hydrosulfite solution caused a quantitative reduction of the tetrazolium to formazan. After one-half minute, 8.5 ml. of acetone was added to each tube, and, after mixing, the solutions were filtered. The color intensities of the filtrates were read against the blank at 470 $\mu\mu$. The average difference between duplicate analyses of pure tetrazolium solutions was 5.8 per cent.

A standard curve obtained as described above is reproduced in figure 1. The readings show a satisfactory degree of linearity in the range of tetrazolium concentrations used (0.02 to 0.10 mg. of triphenyl tetrazolium chloride in 10 ml. volume of solution).

Comments on the technique:

The addition of formaldehyde solution to the samples at the end of the experiments to stop the enzyme activity, as employed in previous modifications of the method, was not found necessary, since it was ascertained in separate experiments that no

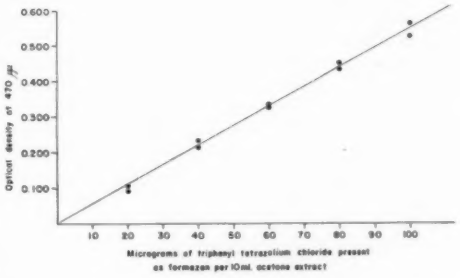

Fig. 1. Tetrazolium standard curve, prepared as described in text.

further tetrazolium reduction occurred during exposure of the tissue to acetone. The rinsing of the tissue samples with water at the end of the experiments helped notably to prevent the development of turbidity during the subsequent extraction with acetone, probably through removal of salts adhering to the tissue surface and to the inside of the tubes. It was found that such rinsing did not remove any of the formazan formed.

The completeness of the extraction of formazan from the tissue was tested by subjecting the samples to treatment with a third portion of acetone. The third acetone extract consistently gave a zero reading.

In the present procedure filtration of the acetone extracts through filter paper was substituted for centrifugation of the acetone samples because it was found that crystal clear filtrates were obtained more readily in this way. Experiments on both standard formazan solutions and on formazan acetone tissue extracts showed that no change in the optical density of the solutions occurred as the result of the filtration. It was further found that the color of the acetone solutions remained unchanged for at least 24 hours when the extracts were kept in the dark in the refrigerator.

A study was made of the rate of diffusion of triphenyl tetrazolium chloride into the aortic tissue. For this purpose an aortic intima-media membrane of 0.73 mm. thickness was inserted into a diffusion apparatus of the type described by Kirk and Johnsen (6). A 1.0 per cent solution of triphenyl tetrazolium chloride in phosphate buffer was placed in one of the

compartments of the apparatus and buffer solution in the other compartment. Samples of the recipient solution were collected at one minute intervals and were tested for the presence of tetrazolium by addition of sodium hydrosulfite. Penetration of tetrazolium through the membrane was noticeable after three minutes, at which time a tetrazolium concentration in the recipient solution of 0.4 micrograms per milliliter was found. Determination of the diffusion coefficient for triphenyl tetrazolium chloride at 39 C. revealed a value of 0.00010.

An investigation was further made of the relation between the length of the experiment and the quantity of tetrazolium reduced by the tissue. For this purpose samples from the same aorta were incubated with triphenyl tetrazolium solution, succinate substrate solution, and phosphate buffer for periods of 20, 40, and 60 minutes. It was found that the average formazan formation during the first, second, and third 20-minute period valued 18, 38, and 44 per cent, respectively, of the amount of formazan formed during the one hour experimental period. Since the relation between time and tetrazolium reduction under the experimental conditions used is not a straight line the actually observed 40-minute formazan values will be reported.

The aortic samples used in the present investigation consisted of intima-media preparations. It was found that tetrazolium reduction occurred in both the intima and media, as evidenced by formazan staining of these layers. Inspection of the aortic samples after the experiments in several instances showed that some areas of the same preparation were deeper stained by formazan than other areas, suggesting an unequal enzyme activity in different parts of the vessel.

The reproducibility of the results of the tissue experiments was determined by carrying out determinations on the tetrazolium reduction in succinate-phosphate buffer medium on 8 different tissue samples from the same aorta. A coefficient of variation of 16.1 was found. This variability may in part be due to uneven distribution of the enzyme activity.

Results

The results of experiments with 35 human aortic samples, using glucose, lactate, pyruvate, acetate, citrate, alpha-ketoglutarate, succinate, l-malate, and oxalacetate as substrates are presented in table 1.

It will be seen from the table that the tetrazolium reduction in the absence of added substrate usually was moderate. With regard to the individual substrates the tissue samples from different subjects often showed considerable variation in the quantity of tetrazolium reduced. No certain correlation was observed between the age of the individuals from whom the samples were derived and the quantity of formazan produced by the tissue. It will be noted from the data listed in the table that in the majority of the experiments the formazan formation in succinate medium exceeded the tetrazolium reduction in the other substrate media. Thus the average formazan formation in glucose, lactate, pyruvate, acetate, citrate, alpha-ketoglutarate, l-malate, and oxalacetate media valued, respectively 12, 30, 21, 20, 47, 71, 39, and 41 per cent of that observed in succinate medium.

The notable degree of tetrazolium reduction by human aortic tissue in the presence of succinate is illustrated in figure 2, which is a reproduction of a photograph of 3 adjacent aortic segments from an 18 year old man, obtained after forty minutes' incubation of the tissue samples with triphenyl tetrazolium chloride in phosphate buffer, citrate medium, and succinate medium.

In order to investigate the stability of the aortic succinic dehydrogenase during storage of the tissue at refrigerator temperature (4 C.) the formazan formation by the aortic tissue was examined at various intervals. It was found that the decrease after two days of storage averaged 20 per cent, and after six days of storage 50 per cent.

In a limited number of the experiments additional studies were carried out on the tetrazolium reduction by the aortic tissue in cis-aconitate, iso-citrate, and fumarate media. The mean formazan formation in the presence of these substrates valued, respectively, 53, 51, and 11 per cent of that in succinate medium.

Discussion

Previous investigations on the reduction of tetrazolium compounds by arterial tissue have been limited to observations on histologic preparations and have not included extraction and quantitative estimation of the amount of formazan produced. In most instances the observations on the arterial tissue have been incidental to some other study.

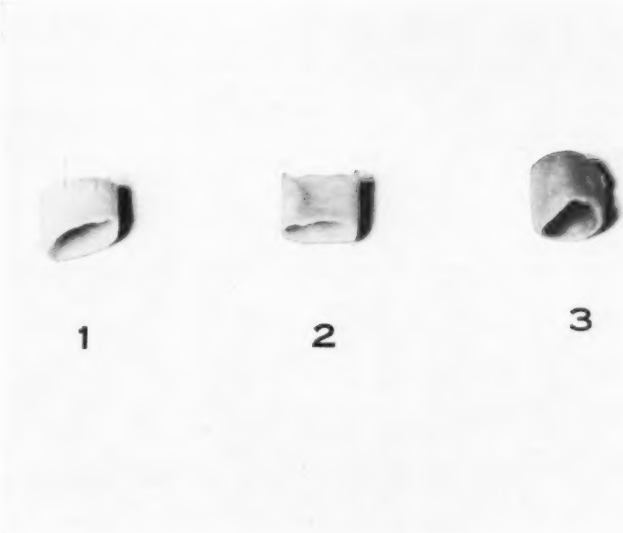

Fig. 2. Photograph of thoracic aorta from an 18-year old man, obtained after forty minutes' incubation of the samples with triphenyl tetrazolium chloride in phosphate buffer solution (1), citrate medium (2), and succinate medium (3).

TABLE

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TABLE 1. FORMAZAN FORMATION FROM TRIPHENYL TETRAZOLIUM CHLORIDE BY HUMAN AORTIC TISSUE IN THE PRESENCE OF VARIOUS SUBSTRATES.

Values represent milligrams of formazan formed by 1 Gm. of wet tissue in a 40-minute experimental period at 39 C.

No.	Sex	Age in Years	None	Glucose	Lactate	Pyruvate	Acetate	Citrate	Alpha-Ketoglutarate	Succinate	l-Malate	Oxalacetate
1	M	0.3	0.000	.....	.....	.....	0.047	0.019	0.036	0.107	.....	0.024
2	F	2	0.004	0.019	0.000	0.000	0.039	0.037	0.044	0.037	0.051	0.027
3	M	3	0.001	0.007	0.010	0.000	0.055	0.037	0.042	0.059	0.021	0.029
4	M	4	0.000	0.009	.....	0.011	.....	.....	0.023	0.130	0.013	.....
5	M	18	0.002	0.004	0.006	0.002	0.007	0.089	0.030	0.196	0.026	0.011
6	F	24	0.025	0.012	0.002	0.003	0.016	0.014	0.016	0.015	0.032	0.048
7	M	30	0.022	0.027	0.121	0.007	0.008	0.076	0.232	0.181	0.056	0.076
8	M	30	0.010	0.019	0.073	0.047	0.034	0.112	0.163	0.189	0.112	0.068
9	M	35	0.005	0.011	0.015	0.000	0.023	0.057	0.038	0.168	0.018	0.018
10	F	38	0.002	0.003	0.002	.....	0.018	0.001	.....	0.020	0.008	.....
11	F	46	0.002	0.031	0.004	0.002	0.007	0.005	.....	0.089	0.006	0.008
12	F	49	0.011	0.006	0.004	0.000	0.003	0.042	0.029	0.075	0.011	0.022
13	F	51	0.001	0.001	0.001	0.003	0.011	0.002	0.016	0.030	0.003	0.007
14	M	52	0.123	0.027	0.341	0.244	0.125	0.471	0.494	0.795	0.378	0.266
15	M	53	0.007	0.020	0.000	0.015	0.002	0.005	0.005	0.039	0.011	0.012
16	M	54	0.002	0.003	0.001	.....	0.003	0.002	.....	0.021	0.003	.....
17	F	54	0.005	0.011	0.000	.....	0.007	0.000	.....	0.088	0.000	.....
18	M	54	0.001	0.000	0.003	.....	0.005	0.006	.....	0.013	0.003	.....
19	F	56	0.000	0.001	0.023	.....	0.003	0.001	.....	0.045	0.002	.....
20	M	58	0.041	0.044	0.029	.....	0.031	0.039	.....	0.072	0.047	.....
21	M	58	0.000	0.005	0.003	0.004	0.003	0.004	0.010	0.046	0.000	0.008
22	M	58	0.011	0.009	0.011	0.004	0.004	0.053	0.027	0.081	0.005	0.018
23	M	59	0.026	0.014	0.054	0.052	0.060	0.140	0.196	0.218	0.136	0.129
24	M	60	0.012	0.002	0.006	0.013	0.014	0.011	0.010	0.042	0.016	0.015
25	M	61	0.002	0.002	0.002	0.001	0.003	0.002	0.006	0.023	0.000	0.013
26	M	62	0.005	0.001	0.012	0.013	0.009	0.017	0.042	0.044	0.001	0.013
27	M	65	0.013	0.009	0.010	0.004	0.006	0.013	0.007	0.025	0.008	0.009
28	M	67	0.014	0.011	0.018	0.023	0.021	0.062	0.042	0.077	0.021	0.033
29	F	70	0.006	0.013	0.012	0.007	0.006	0.011	0.009	0.040	0.006	0.036
30	M	71	0.006	0.006	0.005	0.006	0.012	0.013	0.023	0.037	0.021	0.010
31	M	71	0.026	0.017	0.017	0.017	0.013	0.041	0.076	0.143	0.046	0.018
32	M	71	0.008	0.002	0.002	0.000	0.007	0.006	0.034	0.059	0.009	0.003
33	M	72	0.046	0.008	0.115	0.079	0.035	0.175	0.216	0.146	0.161	0.112
34	M	73	0.033	0.042	0.110	0.052	0.040	0.088	0.206	0.242	0.133	0.138
35	M	85	0.021	0.032	0.044	0.004	0.040	0.036	0.037	0.135	0.055	0.047
Mean			0.014	0.013	0.032	0.022	0.021	0.050	0.076	0.107	0.042	0.044

Rutenburg, Gofstein, and Seligman (9) after intraperitoneal injection of ditetrazolium to mice observed no staining of the vessel walls either in the kidney or the liver. In contrast to this Black, Opler, and Speer (2) in histochemical studies on normal and diseased human tissues found minimal coloration of all layers of the aorta after incubation of the tissue for thirty minutes in a 1 per cent solution of triphenyl tetrazolium chloride. Neumann and Koch (8) have reported studies in which slices of dog, rabbit,

guinea pig, and mouse organs were immersed in a buffered solution of succinate and 4,4,-bis-(3,5-diphenyl-2-tetrazolium) biphenylene chloride. No tetrazolium reduction was noted in the aorta after four hours' incubation in this medium, whereas a moderate formazan formation was found in the muscular layers of middle-sized and small arteries and veins.

The demonstration in the present study of a higher rate of tetrazolium reduction by human aortic tissue following incubation in solutions of various intermediates of the tricarboxylic acid cycle than in glucose medium points to the presence in the tissue of dehydrogenases directed towards these compounds. Of particular importance in this respect are the observations made on samples No. 14 and 33. In the experiments with these aortic samples a considerable formazan formation was found not only in succinate medium, but also in lactate, pyruvate, acetate, alpha-ketoglutarate, l-malate, and oxalacetate media. The aortic preparations in these 2 cases were obtained at autopsies performed less than one hour after the traumatic death of the individuals.

The rather low formazan formation by several of the aortic samples in some of the substrate media used may be due to a partial destruction of the respective dehydrogenases or their coenzymes after death. The importance of the coenzyme level in the tissue for the rate of tetrazolium reduction is suggested by the data in table 1, which show that the formazan formation caused by coenzyme dependent enzymes on the whole are of the same order of magnitude for the individual aortic samples (e.g., the formazan formation in citrate, alpha-ketoglutarate, l-malate, and oxalacetate media). It has been shown (4) that succinic dehydrogenase is more resistant to destruction than the other dehydrogenases of the tricarboxylic acid cycle. The data reported in the present investigation on the effect of storage on the aortic succinic dehydrogenase activity likewise have revealed a fair stability of the enzyme. This fact, together with the independence of succinic dehydrogenase on coenzymes, might explain, at least to some extent, the usually higher values for tetrazolium reduction observed in the present study in succinate medium than in the other substrate media.

Although a low formazan formation by aortic samples obtained several hours after death may be due to a partial destruction of the enzymes or their coenzymes occurring postmortally, the possibility remains that in some instances a decrease in the activities of some of the dehydrogenases was present before death. The low tetrazolium reduction values observed in the case of sample No. 32 would tend to support such contention. This sample was obtained from a 71-year old man within one hour following his sudden death from acute coronary thrombosis. For further elucidation of this subject more extensive studies are required including attempts at reconstituting the coenzyme dependent enzyme systems through addition of coenzymes and cofactors.

Summary

Measurements were made by means of a quantitative tetrazolium technique of the activities of various dehydrogenases in human aortic tissue. The experiments were performed on 35 aortic samples derived from individuals ranging in age between 4 months and 85 years. Glucose, lactate, pyruvate, acetate, and intermediate compounds of the tricarboxylic acid cycle were used as substrates.

In the majority of the samples a notable succinic dehydrogenase activity was found. In some specimens obtained shortly after accidental death a significant formazan formation by the aortic tissue in citrate, alpha-ketoglutarate, l-malate, and oxalacetate media was likewise observed.

The significance of these findings is discussed.

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THE PRESENCE OF ACONITASE AND FUMARASE IN HUMAN AORTIC TISSUE*

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In a study from this laboratory (4) the presence in human aortic tissue of various dehydrogenases associated with the tricarboxylic acid cycle was demonstrated through investigations carried out on the intact tissue with a quantitative tetrazolium technique. The present publication deals with the demonstration of aconitase and fumarase activities in aortic homogenates.

Aconitase

Methods

Seventeen samples of human thoracic aortas were obtained fresh at autopsy at the St. Louis City Morgue† and immediately after removal placed in sterile beakers immersed in crushed ice. The age of the individuals from whom the samples were derived ranged between 7 weeks and 72 years. After removal of the adventitia the aortic tissue was rinsed with water to remove adherent blood and was subsequently homogenized in a pyrex grinder with 9 volumes of 0.1 M phosphate buffer, pH 7.4, making a 10 per cent homogenate.

Determination of the aconitase activity of the homogenates was carried out essentially as described by Johnson (3) by measurement of the quantities of citrate formed from cis-aconitate. For each experiment 4 tubes (150 x 25 mm.) were prepared, 2 of which served as blanks. Four ml. of 0.1 M phosphate buffer, pH 7.4, and 4.0 ml. of 0.1 M cis-aconitic acid, adjusted with sodium hydroxide to pH 7.4, were pipetted into each test tube. To the 2 blanks 20.0 ml. of 20 per cent trichloroacetic acid were further added, after which the tubes were preheated in a water bath at 39 C. for fifteen minutes. At the start of the experiment 2.0 ml. of homogenate and 2.0 ml. of distilled water were added to 1 of the test samples and to 1 of the blanks, and 4.0 ml. of homogenate to the other test sample and to the other blank. The tubes were then allowed to remain in the water bath for exactly thirty minutes. At the end of this period the enzyme activity was stopped in the 2 test samples by addition of 20.0 ml. 20 per cent trichloroacetic acid.

The samples were filtered through Whatman No. 4 filter paper, and the filtrate collected in 250 ml. Erlenmeyer flasks. The test tubes were rinsed with successive small portions of water, and the rinse water likewise passed through the filter papers. The determination of citric acid was carried out on each filtrate essentially as described by Pucher, Sherman, and Vickery (8). Chilled sodium sulfide solution was used for extraction of the pentabromoacetone as recommended by Natelson, Logovyi, and Pincus (7). For colorimetric estimations a Coleman No. 14 spectrophotometer was employed, using a wave length of 430 $\mu\mu$. The samples were read against a tube containing a mixture of sodium sulfide solution and pyridine in the same proportion as in the test samples (7). The average analytic error in determinations on pure citric acid solutions was 5.1 per cent.

An investigation was made of the relation between the length of the experiment and the quantity of citric acid formed by the tissue. For this purpose aliquots of an aortic homogenate were incubated with cis-aconitate solution and phosphate buffer for periods of 15, 30, 45, and 60 minutes. The amounts

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of citric acid produced by 1 Gm. of wet tissue after these incubation periods valued respectively 0.8, 1.7, 2.4, and 4.2 mg.

The relation observed between the amount of tissue in the sample and the quantity of citric acid produced may be seen from the data included in table 1. The degree of proportionality found must be considered as satisfactory.

Experiments conducted on human blood by the same technique failed to reveal aconitase activity, for which reason the possibility of error resulting from inclusion of small amounts of blood in the aortic homogenates can be disregarded. It should be mentioned in this connection that Johnson (3) likewise failed to demonstrate aconitase activity in a study on rat erythrocytes.

Results

The results of aconitase activity determinations on the 17 aortic samples are presented in table 1. It will be seen from the table that the quantity of citric acid formed under the conditions of the experiments ranged between 1.6 and 6.7 milligrams per gram of wet tissue per hour, with an average value of 4.1 milligrams. The coefficient of correlation: age/citric acid formation, for the present series is -0.16 ($t = 0.63$).

The effect on the aconitase activity of storage of the aortic tissue at 4 C. was examined in 5 samples. The average decrease observed after 1, 2, 5, and 7 days of storage valued respectively 44, 50, 60, and 84 per cent.

TABLE 1. ACONITASE ACTIVITY OF HOMOGENATES OF HUMAN AORTIC TISSUE.

Number	Sex	Age in Years	Milligrams of Citric Acid Formed by 1 Gm. of Wet Tissue per Hour		
			I‡	II†	Average
1	M	0.13	.....	4.6	4.6
2	F	4	5.6	7.7	6.7
3	M	29	5.1	5.8	5.5
4	F	29	2.4	2.1	2.3
5	M	30	3.4	3.5	3.5
6	M	42	3.4	4.2	3.8
7	M	43	1.6	1.6	1.6
8	M	43	5.2	5.7	5.5
9	M	47	5.6	5.8	5.7
10	F	51	2.4	2.5	2.5
11	M	55	3.8	3.9	3.9
12	M	58	2.7	3.0	2.9
13	M	59	3.5	4.3	3.9
14	M	63	5.0	6.0	5.5
15	M	65	4.3	5.2	4.8
16	M	69	3.1	3.6	3.4
17	M	72	4.0	3.2	3.6
		Mean			4.1

‡ 2.0 ml. 10 % homogenate used in experiment.
† 4.0 ml. 10 % homogenate used in experiment.

FUMARASE

Methods

Investigations on the fumarase activity of human aortic tissue were performed on 21 samples. The age of the individuals from whom the aortas were obtained ranged between 2 and 82 years. The preparation of the tissue and of the homogenates was similar to that described for the aconitase technique, except that 0.03 M phosphate buffer, pH 6.7, was used as homogenizing medium. Special care was exercized to remove blood adhering to the tissue by rinsing of the samples before homogenization.

The determination of the fumarase activity of the homogenates was carried out essentially as described by Lowry and associates (6) by measurement of the quantities of l-malic

acid formed from fumarate. For the sake of convenience the procedure was performed on a macro scale rather than by micro technique. The substrate reagent used was a 0.05 M solution of sodium fumarate in 0.03 M phosphate buffer; the pH of the reagent was adjusted to 6.7. The beta-naphthol solution employed was prepared from beta-naphthol purified by recrystallization.

For each experiment 4 tubes (150 x 20 mm.) were prepared, 2 of which served as blanks. Four and one-half ml. of substrate reagent and 0.5 ml. of 0.1 N sodium arsenite solution were pipetted into each tube. To the 2 blanks 3.0 ml. of 50 per cent trichloroacetic acid were further added, after which the tubes were preheated in a water bath at 39 C. for fifteen minutes. At the start of the experiment 1.0 ml. of homogenate was added to 1 of the test samples and to 1 of the blanks, and 2.0 ml. of homogenate to the other test sample and to the other blank. The volumes in the tubes containing 1.0 ml. of homogenate were made up to 10.0 ml. by addition of 1.0 ml. of distilled water. The tubes were then left in the water bath for exactly thirty minutes. At the end of this period the enzyme activity was stopped in the 2 test samples by addition of 3.0 ml. of 50 per cent trichloroacetic acid.

For malic acid determination the samples were filtered through Whatman No. 2 filter paper. Fifty cubic millimeters of each filtrate were then pipetted into a 150 x 20 mm. carefully cleaned test tube by means of a constriction pipette. To this sample was added 5.0 ml. of the combined sulfuric acid-beta-naphthol reagent described by Lowry and his associates (6). The content of the tubes was carefully mixed, and the tubes stoppered by aluminum foil-covered cork stoppers. For development of fluorescence the tubes were subsequently heated in a boiling water bath for thirty minutes and were afterwards cooled to room temperature. The fluorescence of the samples and the blanks was finally measured against a quinine sulfate standard (1.0 milligram per cent solution of quinine sulfate in 0.1 N sulfuric acid) in a Farrand photoelectric fluorometer, using 3.0 ml. cuvettes.

The malic acid content of the samples was estimated by comparison of the fluorometer readings with those obtained by analysis of standard l-malic acid solutions of suitable concentrations. For construction of the standard curve 50 cu. mm. of 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 mM l-malic acid solutions were analyzed as described above. A representative malic acid standard curve obtained in this way is shown in figure 1. It will be noted that the curve is not linear. The reproducibility of the curve was, however, found to be very satisfactory. The average analytic error in determinations on pure malic acid solutions within this concentration range was 4.0 per cent.

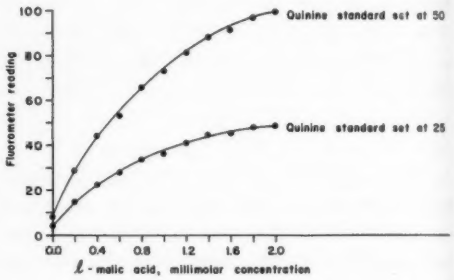

Fig. 1. Fluorometric standard curve for l-malic acid. The quinine standard used contained 1.0 milligram of quinine sulfate in 100 ml. of 0.1 N sulfuric acid. The analytic procedure employed in construction of the curve is given in the text.

An investigation was made of the relation between the length of the experiment and the quantity of malic acid formed by the tissue. For this purpose 1.0 and 2.0 ml. aliquots of an aortic homogenate were incubated with sodium fumarate solution, phosphate buffer, and sodium arsenite for periods of 15, 30, 45, and 60 minutes. The amounts of malic acid produced per gram of wet tissue after these incubation periods valued respectively 2.5, 4.0, 6.6, and 8.7 milligrams with the use of 1.0 ml. homogenate aliquots, and 2.4, 4.2, 4.8, and 5.5 milligrams with the use of 2.0 ml.

homogenate samples. A satisfactory degree of proportionality between time and the quantity of malic acid formed was thus observed for the 1.0 ml. homogenate samples over the whole one hour period, and for the 2.0 ml. samples for the first 30-minute period of incubation.

The relation observed between the amount of tissue in the sample and the quantity of malic acid formed under the conditions of the test (thirty minute incubation period) may further be seen from the data included in table 2. The proportionality found for the test period used must be considered as satisfactory.

Experiments conducted on human blood by the same technique showed a notable fumarase activity, the amount of malic acid formed by 1.0 ml. of whole blood per hour being approximately 2.0 milligrams. Since careful rinsing of the aortic samples was made before the homogenization of the tissue, a correction for the fumarase activity of the minute amounts of blood occasionally contained in the samples was not made because it was estimated to be well within the experimental error of the procedure.

Results

The results of fumarase activity determinations on the 21 aortic samples are presented in table 2. It will be seen from the table that the quantity of l-malic acid formed under the conditions of the experiments ranged between 3.4 and 11.9 milligrams per gram wet tissue per hour, with an average value of 8.0 milligrams. A calculation of the coefficient of correlation: age/l-malic acid formation, for the present series revealed a significant degree of correlation, the r value being -0.62 ($t = 3.43$).

The effect on the fumarase activity of storage of the aortic tissue at 4 C. was examined in 4 samples. It was found that no measurable change in activity occurred during the first 24 hours of storage, and that the decrease in activity after 5 days averaged only 9 per cent.

TABLE 2. FUMARASE ACTIVITY OF HOMOGENATES OF HUMAN AORTIC TISSUE.

Number	Sex	Age in Years	Milligrams of l-Malic Acid Formed by 1 Gm. of Wet Tissue per Hour		
			I‡	II†	Average
1	M	2	11.8	11.0	11.4
2	F	23	12.4	10.2	11.3
3	M	27	12.4	11.4	11.9
4	F	44	10.2	8.0	9.1
5	M	44	11.8	11.0	11.4
6	M	45	9.6	8.2	8.9
7	F	50	6.0	5.8	5.9
8	F	51	11.0	11.0	11.0
9	M	53	8.4	8.6	8.5
10	M	58	6.0	6.0	6.0
11	M	59	3.2	3.6	3.4
12	M	60	7.0	7.0	7.0
13	M	60	8.0	7.2	7.6
14	M	61	8.0	8.2	8.1
15	M	62	6.0	6.4	6.2
16	M	66	7.8	7.0	7.4
17	M	67	6.8	7.8	7.3
18	F	67	3.0	2.2	2.6
19	M	68	8.0	7.0	7.5
20	M	71	9.8	6.2	8.0
21	F	82	8.0	7.8	7.9
		Mean			8.0

‡ 1.0 ml. 10 % homogenate used in experiment.
† 2.0 ml. 10 % homogenate used in experiment.

Discussion

Aconitase and fumarase represent enzyme systems, which catalyze specific hydration-dehydration processes. Since these processes constitute important steps in the tricarboxylic acid cycle, the demonstration of these 2 enzymes in the aortic tissue forms an important support for the supposition that this cycle is operating in human aortic tissue.

A comparison of the activities of aconitase and fumarase in human aortic tissue with the concentration in other human organs is rendered difficult by the general lack of information concerning the concentration of these enzymes in human tissues. The aconitase activity observed for human aortic tissue in the present study is of the same order of magnitude as that found for rabbit bone marrow by Goldinger, Lipton, and Barron (2) and is approximately 3 and 8 per cent, respectively, of the activity reported for rat and rabbit kidney and liver by Dixon and Perkins (1). Similarly, the fumarase activity of human aortic tissue is about 2 per cent of that observed by Lowry and his associates (5) for the rabbit brain.

No significant correlation was observed in the present investigation between the age of the individuals from whom the aortic preparations were obtained and the aconitase activity of the samples. In contrast to this, a significant negative relation was found between age and the fumarase activity of the aortic homogenates. It seems possible that the stability of the aortic fumarase, as observed in the present study, may have been a factor of importance in disclosing such correlation between age and tissue enzyme concentration. In view of the significance of this finding a more extensive study of the subject is being undertaken.

Summary

Measurements were made of the aconitase and fumarase activities of homogenates prepared from human aortic tissue. The aconitase studies revealed an average formation of 4.1 milligrams of citric acid from cis-aconitate per 1 Gm. of wet tissue per hour. In the fumarase experiments the mean quantity of malic acid formed from fumarate valued 8.0 milligrams per 1 Gm. wet tissue per hour.

A significant negative correlation was observed between the age of the individuals from whom the samples were derived and the fumarase activity of the tissue ($r = -0.62$, $t = 3.43$).

The demonstration of the presence of aconitase and fumarase in human aortic tissue constitutes an important support for the assumption that the tricarboxylic acid enzyme cycle is operating in the tissue.

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AGE CHANGES IN BASAL RESPIRATORY MEASUREMENTS AND METABOLISM IN MALES

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OUR knowledge of the effects of age on basal respiratory measurements is extremely scanty. The most recent surveys of physiologic changes with age (5, 14, 33) give no information about respiratory rate, volume, tidal volume, or the effectiveness of oxygen (O_2) uptake and carbon dioxide (CO_2) elimination from the lungs. Although standard values of basal O_2 uptake and heat production are used clinically, examination of the data shows that very few actual observations have been made on subjects over the age of 65 (28). In the series reported by Boothby, Berkson, and Dunn (9) no males over age 65 and only 15 females were tested. In the recent report of Robertson and Reid (26) 16 males and 25 females over age 65 were measured. With the exception of Lewis (21) and Kountz, Chieffi, and Kirk (20), no systematic observations on O_2 uptake in elderly subjects have been reported although studies on small isolated groups of older subjects may be found in the literature (1, 4, 6, 7, 8, 19, 23, 27). The following study was carried out in order to fill some of the gaps in our knowledge of respiratory function in the aged male.

METHODS

Subjects: Tests were performed on 152 male subjects selected from the Infirmary Division (Old People's Home) of the Baltimore City Hospitals. The subjects ranged in age from 41 to 90 years. The reasons for admission to the Infirmary for custodial care are socio-economic rather than medical. All subjects were ambulatory and had been in the Infirmary or on the wards of the Section on Gerontology for at least a month prior to testing. Each subject was examined clinically and none were admitted to the study who gave clinical evidence of hyperthyroidism, myxedema, renal disease, diabetes, or cardiac failure. Patients who had received iodine or thyroid medication were excluded from the study. All subjects had blood pressures less than 180/95 mm. Hg and oral temperatures below 99° F. on the mornings of the tests.

Methods: All tests were performed by the Tissot open circuit method (24) with analysis of the expired air for CO_2 and O_2 content by the Haldane method. The subject was fitted with a Siebe-Gorman half mask which permitted oro-nasal breathing. The adjustment of the mask was tested for leaks at the end of each collection period. Outdoor air was inspired by the subject and separation of the expired air was made through mercury (Bailey) valves which operated at a pressure of approximately 5 mm. water. Expired air was collected for periods of 6 to 8 minutes. During each period respiration rate was counted for two one-minute periods and pulse rates were counted for two 30-second intervals. Blood pressures were determined by the auscultatory method at the end of each gas collection period.

Experimental Procedure: In order to minimize the effects of apprehension, each subject was exposed to the experimental procedure on two afternoons prior to the basal determinations. All subjects spent the night prior to the tests in the hospital ward of the Section on Gerontology. On the morning of the test, the patient was transferred in bed to the metabolism testing room which was on

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A preliminary report of this study was read at the Fifth Annual Scientific meeting of the Gerontological Society, Inc., September 5-7, 1952 (31), Washington D. C.

the ward. All tests were run between 7 a. m. and 9 a. m. with the patient in a basal state. After recording oral temperature, blood pressure, and pulse rate, the mask was fitted to the patient and tested for leaks. A 10-minute period with the subject breathing outdoor air elapsed before beginning the first collection period. Three 6 to 8-minute periods were then made. Samples of expired air were taken from each period in mercury tubes for Haldane analysis. At the end of the third period the height and weight of the patient was recorded. The same procedure was followed on a second day, within one week of the first.

Calculations: All gas volumes were reduced to O° C., 760 mm. Hg pressure, dry. Expiratory volumes were calculated from the spirometer readings. Tidal volumes were determined by dividing expiratory volumes by the average respiratory rates. Oxygen uptake, CO_2 elimination, and heat production were calculated by standard procedures (24). The factor used for conversion of O_2 uptake to heat production was determined by the experimentally observed R.Q. Average values for all determinations on each of the 2 days were calculated for each subject. The subjects were distributed in 10-year age groups for estimation of mean values by age. Surface area was calculated from height and weight by the DuBois formula (16). All volume measurements as well as O_2 uptake, CO_2 elimination, and heat production were calculated per square meter of surface area, and per kilogram body weight.

An analysis of variance was carried out on all observations as indicated in table 1 (17). The error variance was used to test the significance of the individuals × days interaction. If this test met the criterion of significance at the 0.1 per cent level of probability it was concluded that the day to day variation in the measurement was significant and that individual subjects differ with respect to their day to day fluctuations. The individual × days variance was used to test the significance of the variance within age classes. If this test met the criterion of significance it was concluded that the measurement was capable of detecting individual differences between subjects of the same age range. The variance within age classes was used to test the significance of age changes in the measurement.

TABLE 1. ANALYSIS OF VARIANCE.

Source of Variation	Degrees of Freedom
Among ages	4
Within age classes	147
Between days	1
Interaction	
Age × days (formal)	4
Individuals × days (within age classes)	147
Error (period to period within individuals)	608

Since the analysis of variance gave only an estimate of the significance of age in contributing to the total variance of all measurements, the regression of each measurement on age was computed by the method of least squares (32) using average values for each subject to determine the amount of change with age. The estimated slope of the linear regression coefficient on age was tested against its standard error for significance.

RESULTS

Error of Measurement: The standard errors of measurement of all variables, computed from the analysis of variance are shown in column 1 of table 2. These values represent the discrepancies expected between measurements made on a single day and do not include the variation between days, i.e., any day to day biologic variation. This measurement error ranges from approximately 10 per cent of the mean values

TABLE 2. STANDARD ERRORS OF MEASUREMENT AND MEAN VALUES BY AGE DECADES OF BASAL RESPIRATORY FUNCTIONS IN MALES.

TABLE 2. STANDARD ERRORS OF MEASUREMENT AND MEAN VALUES BY AGE DECADES OF BASAL RESPIRATORY FUNCTIONS IN MALES.

Variable	σ_{est}	Age (Years) 40-49 N = 27		50-59 N = 27		60-69 N = 39		70-79 N = 38		80-90 N = 21	
		Mean	σ_d	Mean	σ_d	Mean	σ_d	Mean	σ_d	Mean	σ_d
Ventilation rate/min.	1.3	16.83	2.756	16.73	2.756	16.92	2.976	18.77	3.658	18.22	2.898
Ventilation Vol. L./min.	0.312	6.899	1.2896	6.947	1.0140	6.708	.9920	6.868	1.2524	6.570	1.3110
Ventilation Vol. L./sq.m./min.	0.440	3.97	.6916	4.03	.6812	3.93	.8556	4.13	.6882	4.03	.7958
Tidal Vol. cc./breath	34.0	422.0	83.2	426.5	72.8	408.3	74.4	377.2	74.4	366.3	64.4
Tidal Vol. cc./sq.m./breath	2.0	242.7	46.8	246.7	41.6	238.5	43.4	226.3	37.2	223.3	27.6
Expired Air % O_2	0.14	17.89	.4368	18.04	.4472	18.12	.3038	18.28	.3472	18.43	.3496
Expired Air % CO_2	0.09	2.58	.3224	2.52	.3744	2.44	.2604	2.26	.3162	2.14	.2714
CO_2 Elimination cc./min.	8.6	173.38	21.32	171.03	20.28	159.90	21.08	150.92	26.04	138.93	25.30
CO_2 Elimination cc./Kg./min.	0.014	2.72	.3276	2.72	.4472	2.51	.3720	2.49	.2976	2.34	.3496
CO_2 Elimination cc./sq.m./min.	5.0	99.68	9.464	98.92	12.220	93.42	10.850	90.47	11.346	84.60	11.086
Oxygen Uptake cc./min.	10.9	215.07	32.24	210.88	33.28	193.23	26.66	188.30	29.14	171.92	33.58
Oxygen Uptake cc./Kg./min.	0.018	3.37	.416	3.35	.572	3.03	.434	3.12	.434	2.89	.460
Oxygen Uptake cc./sq.m./min.	6.4	123.45	14.56	121.88	18.20	112.88	13.02	113.08	13.02	104.68	16.10
Heat Production cal./sq.m./hr.	1.7	35.73	3.952	34.50	4.472	33.00	3.596	32.60	3.720	30.05	4.646

σ_{est} = standard error of measurement

σ_d = standard deviation of the distribution

TABLE 3. SUMMARY OF ANALYSIS OF VARIANCE.

Variable	Units	Source of Variance: Among Ages 4 df†		Within Ages 147 df†		Individuals x Days 147 df†		Error 608 df†
		MS‡	f§	MS‡	f§	MS‡	f§	MS‡
Respiration	rate/min.	169.84	2.96*	57.31	5.7	10.01*	5.7	1.76
Ventilation Vol.	L./min.	3.691	.45*	8.144	12.6	.643	6.4	.097
Ventilation Vol.	L./sq.m./min.	1.276	.42*	2.876	12.4	.232	1.2*	.196
Tidal Vol.	L./breath	.1173	3.49*	.0336	5.02	.0067	5.6	.00118
Tidal Vol.	L./sq.m./breath	.01715	1.76*	.00976	4.21	.00232	5.7	.000404
Expired Air	% O_2	6.4873	7.8	.8385	7.1	.1174	5.8	.0202
Expired Air	% CO_2	5.3001	9.2	.5775	8.7	.0664	7.4	.0090
CO_2 Elimination	cc./min.	30684	9.8	3140	9.1	345.4	4.6	74.7
CO_2 Elimination	cc./Kg./min.	4.0672	5.2	.780	9.0	.0862	4.6	.0187
CO_2 Elimination	cc./sq.m./min.	5760	7.9	729.9	6.3	115.5	4.6	25.0
O_2 Uptake	cc./min.	45793	8.3	5541	17.7	313.4	2.6	119.7
O_2 Uptake	cc./Kg./min.	6.6576	5.1	1.315	16.2	.0813	2.6	.0310
O_2 Uptake	cc./sq.m./min.	8614	6.5	1325	12.4	107.3	2.6	41.17
Heat Production	cal./sq.m./hr.	661.5	6.8	96.6	12.5	7.74	2.7	2.87

* Values not meeting criterion of significance

† df = degrees of freedom

‡ MS = mean squares

§ f = f ratio. An f ratio is judged significant if $P \leqq 0.001$. The minimum values of f required for significance are 4.62; 2.5 and 2.5 for variance among ages, within ages, and individuals × days, respectively. The values of 2.5 are based on only 20 and 120 degrees of freedom.

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for ventilation volume to 0.8 per cent of the mean value for the percent O_2 in expired air. However, the analysis of variance summarized in table 3 indicates that in all variables listed, the measurement error is significantly smaller than the variation between individuals (within ages variance). Since the individual × days interaction shown in table 3 is significant (except for ventilation volume in liters per square meter per minute) it may be concluded that individual differences in variation between measurements made on different days can be identified.

Age Changes: Average values, by decades of chronologic age, are summarized in table 2. Inspection of the mean values shows no evidence of a systematic age change in respiratory rate, ventilation volume, tidal volume, or pulse rate. In contrast there is a progressive rise in the percent O_2 and a fall in the percent CO_2 in expired air, CO_2 elimination, O_2 uptake, and calculated heat production. The decrement in CO_2 excretion and O_2 uptake remains even after correction for body size is made. Because of the wide individual differences in all of the respiratory measurements, differences between adjacent age decades are apparently not significant.

The analysis of variance, summarized in table 3, indicates that age contributes significantly to the total variance of the CO_2 and O_2 content of the expired air, the CO_2 elimination, O_2 uptake, and the heat production, but not to respiratory rate or volumes (column 1—Variance among ages).

An estimate of the average rate of change in the variables showing a significant contribution of age is provided by the values of the slope of the linear regression equation (the value of b in the equation $y = bx + c$, where y is the value at age x in years). The slope values (b) with their standard errors, are shown in table 4. The negative signs indicate a decrement in average values with age. For example, the CO_2 elimination falls at the rate of approximately 9 cc. per minute per decade, and the basal heat production about 1.37 cal./sq.m./hour for each 10 years' increase in age. Although small, all of the changes are significant as shown by the t values in the last column of table 4.

Discussion

Examination of all the available data shows that the decrement in basal metabolism with age is significant. The fall in average values is corroborated by measurements made at intervals of 14 to 50 years in the same subject. Magnus-Levy (22) has reported values on himself and 4 other investigators with the following results; Professor Zuntz at age 41, BMR = 33.6 cal./sq.m./hr., at age 70, 30.2; Professor Magnus-Levy at age 26, 38.1 cal./sq.m./hr., at age 76, 31.5; Professor Lusk at age 44, 42.8 cal./sq.m./hr., at 58, 32.7; Professor Benedict, at age 38, 38.2 ca[1]./sq.m./hr., at 57, 32.7; Professor DuBois at age 30, 38.1 ca[1]./sq.m./hr., at 58, 34.5.

Turovetz (34) has reported extremely low values (11.5—31.7 ca[1]./sq.m./hr.) in a series of 12 Russian males between the ages of 95 and 142 years. Ages are estimated within a 5 year span and no information about the general health or activity of the subjects is given.

It is clear that the values reported in the older literature are significantly higher than those obtained in more recent studies (15). Thus the Boothby, Berkson, and Dunn values are lower than those first reported by Aub and DuBois (2). Furthermore a comparison of the values reported by Lewis (21) with those obtained in the present study shows a significant difference in the slope of the regression of basal heat production on age. Although the mean values at age 50 to 59 are the same for both studies, they diverge with increasing age to 3.5 cal./sq.m./hr. at age 80 to 89. The regression equation for the Lewis data is cal./sq.m./hr. = 39.133 −0.0678 age; whereas the data from the present study give the equation cal./sq.m./hr. = 41.5 −0.137 age. Thus the average rate of fall in basal metabolism in the Baltimore population was twice as fast as that observed in the New York group. This may

† MS = mean squares
§ f = f ratio. An f ratio is judged significant if $P \leq 0.001$. The minimum values of f required for significance are 4.62; 2.5 and 2.5 for variance among ages, within ages, and individuals × days, respectively. The values of 2.5 are based on only 20 and 120 degrees of freedom.

TABLE 4. SUMMARY OF REGRESSION ANALYSIS OF BASAL RESPIRATORY FUNCTIONS ON AGE

($y = bx + c$, y = value at age $\times$ (yrs.))

Variable	Units	b	σ_b*	t
Expired Air	% O_2	.0136	.0021	6.5
Expired Air	% CO_2	—.0120	.0016	7.5
CO_2 Elimination	cc./min.	—.919	.116	7.9
CO_2 Elimination	cc./Kg./min.	—.0100	.002	5.0
CO_2 Elimination	cc./sq.m./min.	—.400	.067	6.0
O_2 Uptake	cc./min.	—1.121	.110	10.0
O_2 Uptake	cc./Kg./min.	—0.012	.004	3.0
O_2 Uptake	cc./sq.m./min.	—0.476	.065	7.3
Heat Production	cal./sq.m./hr.	—0.137	.017	8.0

* σ_b = standard error of b.

be due to sampling differences; the New York group of aged were still living in the community while the Baltimore subjects were residents of an institution. The Baltimore values are in close agreement with the results obtained by Kountz, Chieffi, and Kirk, who also studied patients in an old people's home (20).

In order to arrive at a composite value for basal metabolism in elderly people, data from a number of studies on institutional populations carried out since 1934 have been summarized in table 5. Weighted mean values were computed and are plotted in figure 1. The regression equation for these values is cal./sq.m./hr. = 40.22 —0.110 age. Figure 1 also shows the regression lines and the mean values for the data of Lewis (21) and of Boothby, Berkson, and Dunn (9). It is of some interest that a detailed statistical analysis of records of basal metabolism of over 8600 subjects collected from the literature of Quenouille, Boyne, Fisher, and Leitch (25) led them to conclude that "when all other variables have been taken into account, the massed data for adults of both sexes and all racial groups analyzed, conform to the rule that basal metabolism declines at the

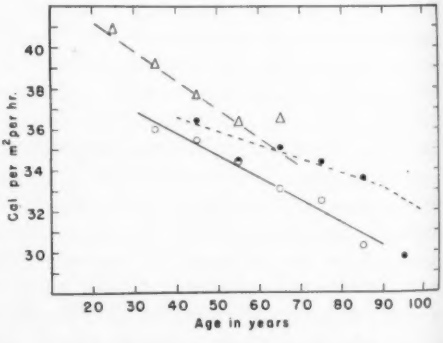

Fig. 1. Linear regression of basal heat production of males on age. Mean values by decades are shown as individual points; Δ - - - - Δ. Data of Boothby, Berkson, and Dunn (9); ● - - - ●. Data of Lewis (21); ○———○. Composite values for subjects (age 30-90) as shown in table 5.

rate of 3 percent per decade from age 3 to over 80." This value would be approximately 1.08 cal./sq.m./hr./decade as compared with the value 1.1 cal./sq.m./hr./decade derived from mean values of table 5.

Linear regressions of basal heat production on age were also derived by Harris and Benedict (18). Their equation, for men expressed in cal./sq.m./hr. is cal./sq.m./hr. $= 42.6 - 0.150$ age.

Other investigators have fitted theoretic curves to basal metabolism data on the assumption that the fall takes place at a constant percentage rate. Thus Brody (12) derived the equation cal./sq.m./hr. $= 56.7\, e^{-0.024A} - 32.0\, e^{-1.224A}$, where e is the base of natural logarithms and A is the age in years. Similarly, Bruen (13) using the data of Aub and DuBois (2, 15) derived the following single exponential equations for men age 20 to 70, cal./sq.m./hr. $= 42.67\ e^{-0.0024\,A}$. The data of Boothby and Sandiford (10) yielded the following equation, cal./sq.m./hr. $= 44.16\ e^{-0.0033A}$. Although the exponential equations have the virtue of a rational approach, the wide dispersion of metabolism observations make it impossible to demonstrate that the fit obtained is significantly better for an exponential curve than for a linear one. Thus, for practical considerations the linear curve is at least as accurate a description of the regression as the exponential and is easier to apply.

Although the mean respiratory rate tended to rise progressively with age the individual variability was so high that the increment was not significant ($P > 0.05$). In 12 men aged 59 to 91 Robinson (27) found no systematic change with age. His values are somewhat lower than ours (average 12.2). The values for our older subjects are also significantly higher than those reported by Shock and Soley (29) on a group of 46 males, aged 27 to 43 years (mean value 13.7).

The absence of changes in resting respiratory volumes with age observed is in accord with the few values reported in the literature. When the values of Robinson (27) are corrected to standard temperature and pressure, the respiratory volume in liters per square meter per minute at ages 50 to 59, 60 to 69 and 70 to 79 were 3.29, 3.07, and 3.22, respectively. Baldwin, Cournand, and Richards (3) observed in 19 males, aged 50 to 69, an average respiratory volume of 3.18 L./sq.m./min. (STP). It is thus apparent that measurements of respiratory volume are influenced by a large number of factors which make a greater contribution to the total variance than does age.

With increasing age there is a significant rise in O_2 content of the expired air and a fall in the CO_2 content. The latter is in agreement with the observations reported by Boyer and Bailey (11), who found a gradual fall in pCO_2 of expired air between the ages of 20 and 65 years. At age 20 to 24 the pCO_2 of expired air was 20.72 mm. Hg as compared with 18.97 mm. Hg in 7 subjects age 65 and over.

The data show clearly that the age-wise diminution in basal oxygen uptake per unit of surface area effects an alteration in oxygen uptake from the inspired air rather than a diminution in the volume of air respired. These results can be explained on the presumption that in the aged subjects an increasing proportion of the inspired air was not effectively exposed to a capillary bed for gas transport. There is, however, no evidence for an accumulation of CO_2 in the older subjects (30). Thus under resting conditions the reduced effectiveness of alveolar ventilation does not impair the excretion of CO_2 produced. The evidence presented indicates a reduction in the basal oxygen uptake per unit of surface area and implies a gradual reduction in the effectiveness of alveolar ventilation with increasing age.

Summary

Estimations of oxygen uptake, carbon dioxide elimination, total respiratory volume, and tidal volume were made under basal conditions by the Tissot open circuit method in 152 ambulatory male subjects between the ages of 41 and 90 years. After preliminary

TABLE 5. BASAL METABOLISM IN MALES (CAL./SQ.M./HR.).

Investigator	Ages (Years)											
	30–39		40–49		50–59		60–69		70–79		80–89	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Kountz, et al. (20)*	9	36.46	6	36.18	19	34.41	19	34.14	16	31.26	8	30.31
Binet, Bochet, & Bourlière (6)									6	31.08	9	29.44
Binet & Bourlière (7)									17	32.80	13	30.47
Binet & Bourlière (8)									12	34.9	11	30.80
Matson & Hitchcock (23)									6	31.2	8	29.3
Aaltonen (1)											6	32.70
Robertson & Reid (26)	204	36.00	52	35.2	17	34.30	17	32.30	7	32.70		
Present Study			27	35.73	27	34.50	39	33.00	38	32.60	21	30.05
Weighted Mean	213	36.01	85	35.44	63	34.42	75	33.13	102	32.53	76	30.35

Cal./sq.m./hr. = 40.22 —0.11 age

* The original data from this study were generously given to us by Dr. J. E. Kirk.

training all subjects were tested on two successive days. Analysis of variance of the observations permit the following conclusions:

(a) With increasing age there is a significant reduction in basal heat production and carbon dioxide elimination. There is a significant increase in pO_2 and a decrease in pCO_2 of expired air with increasing age.

(b) There is no significant age trend in respiratory rate, total ventilation volume or tidal volume.

(c) Day to day variations in all measurements (except total ventilation volume per square meter of surface area) are significantly greater ($P < 0.001$) than errors of measurement.

(d) Individual differences can be identified in all variables measured.

We are grateful to Dr. Max Halperin for leading us through the intricacies of the analysis of variance; to Dr. Donald M. Watkin for the clinical evaluation of the subjects; to Mrs. Elizabeth Strawn for supervision of the nursing services; to Mrs. Elizabeth Benser for computational assistance, and to the technical personnel of the Section on Gerontology for the innumerable Haldane analyses performed.

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BLOOD VALUES OF WOMEN: CHOLESTEROL

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INFORMATION regarding the concentrations of the various constituents found in blood can be a helpful tool in judging the health and nutritional well-being of people. Before such information can be used effectively, the range over which the values for these constituents vary in groups of supposedly normal individuals of various ages needs to be known. Studies of this kind represent one phase of a cooperative research project active in the North Central States which deals with the nutritional status and dietary needs of healthy women, 30 years of age and over.

Cholesterol was one of the blood constituents chosen for study. A considerable volume of information is recorded in the literature on the concentration of total cholesterol in blood serum of men. Similar data for women are not as numerous. It is hoped that the results of the present investigation will be useful in clarifying the range of values characteristic of "normal" women in the different decades of adult life.

METHODS

The subjects participating represented two different groups of women. The first group consisted of 54 women living in Iowa; the second of 130 women living in Nebraska. The subjects ranged in age from 18 to 92 years. The number of women studied in the various age-decades in each of the two states is shown in table 1.

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Some of the data reported in this paper were presented before the American Institute of Nutrition, April 18-22, 1949, by M. R. Gram and R. M. Leverton.

The Iowa women represented area sampling units comprised of clusters of households in the city of Ames and its environs. The Nebraska subjects volunteered to participate in the study and were homemakers, professional women, and business women, all living in Lincoln. The subjects were active women able to participate in home and community activities, and none exhibited any overt symptoms of ill health.

Samples of blood for analysis were drawn after a light breakfast of toast and tea or coffee. It has been demonstrated (14) that "neither the total cholesterol content of the blood serum . . . nor the proportion between the various cholesterol fractions is altered significantly after normal meals."The method described by Sperry and Brand (15) was used for the estimation of the concentration of serum total cholesterol.

Information pertaining to body weight, blood pressure, and basal metabolism was obtained by experienced researchers. The subjects were weighed clothed in light undergarments and without shoes.

Records of weighed food intakes for seven days were available for the Iowa women. The protein and fat intake of each subject was calculated from these records with the use of food composition tables. These figures then were used to study the relation of dietary fat and protein to concentration of cholesterol in blood serum.

RESULTS

Total Cholesterol.—The data presented in table 1 show the mean concentrations of total cholesterol in the blood serum of the women studied in each state together with the standard deviations of the items, *i.e.*, Iowa,

TABLE 1. MEAN CONCENTRATIONS OF TOTAL CHOLESTEROL IN THE BLOOD SERUM OF WOMEN IN IOWA AND NEBRASKA.

Decade of Life (Years)	Ames, Iowa			Lincoln, Nebraska		
	Number of Subjects	Total Cholesterol (mg.%)	Standard Deviation of Items (mg.%)	Number of Subjects	Total Cholesterol (mg.%)	Standard Deviation of Items (mg.%)
20-30	.....	.....	.....	22	163	28.4
30-39	10	176	24.6	18	173	33.6
40-49	16	190	49.3	35	201	31.9
50-59	13	219	36.6	29	234	31.3
60-69	6	250	35.6	12	265	48.7
70-79	8	251	45.4	14	251	42.4
80-90	1	154	.....	.....	.....	.....
Total Number of Subjects	54	.....	.....	130	.....	.....
Mean Values	.....	209	48.3	.....	209	48.2

209.0 ± 48.3 mg. per cent; and Nebraska, 209.0 ± 48.2 mg. per cent. Because statistical analysis indicated no significant difference between the values from the two states, the data were pooled for the analyses herein reported.

The mean concentrations and standard deviations of the total cholesterol in the sera of the 184 women in successive decades of life are shown in table 2 and presented graphically in figure 1. There is an increase in mean concentration of serum cholesterol with each successive decade from 163 mg. per cent for the women 30 to 39 years old to a maximal value of 260 mg. per cent for the women 60 to 69 years old. For the women 70 to 79, the value declines to 251 mg. per cent.

Relation to Other Measurements.—Mean values for body weight, basal metabolic rate, and diastolic blood pressure for the women in each age-decade also are presented in table 2. The mean body weights and the diastolic blood pressures of the subjects in each successive decade of life increase significantly from 20 to 70 years. Values for the mean basal metabolic rates in the various decades are not significantly different.

The relationships between these factors (age, body weight, basal metabolism, and diastolic blood pressure) and serum cholesterol were examined by means of multiple regression. The results of these analyses are summarized in table 3. The multiple correlation coefficients show that about one-fourth of the variation in the serum cholesterol data is attributable to age, weight, basal metabolism and blood pressure ($R^2 = .2700$). However, a comparison of

TABLE 2. CERTAIN PHYSIOLOGIC CHARACTERISTICS AND THE CONCENTRATIONS OF TOTAL CHOLESTEROL IN SERUM OF A GROUP OF WOMEN.

Decade of Life (Years)	Number of Subjects	Mean Age (Years)	Total Cholesterol in Serum (mg./100 ml.)		Mean Body Weight (Pounds)	Mean Basal Metabolism (Cal./sq.m. /hr.)	Mean Diastolic Blood Pressure
			Mean	$s_{\bar{x}}$			
20–29	22	20.0	163	6.1	126	34.0	—(22)
30–39	28	34.1	174	5.7	124	34.0	70(14)
40–49	51	44.3	197	5.3	139	32.3(2)	81
50–59	42	54.6	229	5.1	148	32.0	87
60–69	18	63.4	260	10.4	156	33.2	89
70–79	22	73.2	251	9.6	144	30.4	88 (4)
80–90	1	85.0	154	.....	85	33.9	70
All Subjects	184	47.7	209	.....	139	32.6	83
Means Used in Multiple Regression*	142	52.6	220	.....	143	32.2	84

Data pertaining to some subjects were omitted from the multiple regression because information was lacking for certain items. The figures in parentheses indicate the number of subjects for whom some specific information was missing.

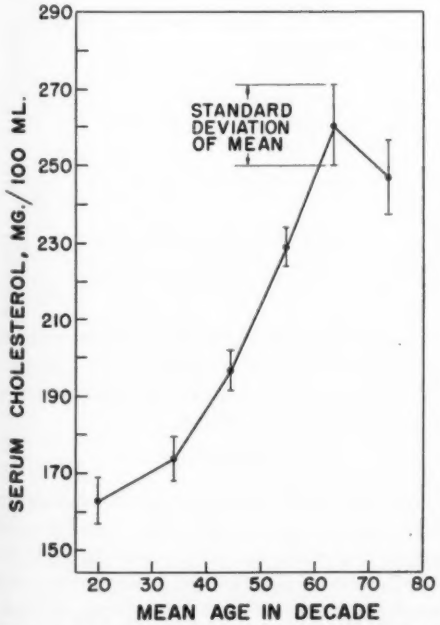

FIG. 1. Mean concentration of total cholesterol in the serum of blood of women in successive decades of life.

TABLE 3. STANDARD PARTIAL REGRESSION COEFFICIENTS OF CONCENTRATION OF TOTAL CHOLESTEROL IN SERUM.

Regression on	Coefficients
Age	+ .4855
Weight	
Basal Metabolism	— .0960
Cal./sq.m./hr.	+ .0017
Diastolic Blood Pressure	+ .1123
n	= 142
R^2	= .2700
(r Cholesterol-Age)^2	= .2529

this value with that of the square of the simple correlation coefficient of cholesterol and age (.2529) indicates that most of the variation that can be accounted for is due to age alone.

Protein and Fat.—In table 4 are shown the mean quantities of protein and fat ingested daily by the Iowa women in the various age-decades, together with the results of a multiple regression designed to show the influence

TABLE 4. MEAN QUANTITIES OF PROTEIN AND FAT INGESTED DAILY BY 54 IOWA WOMEN AND THEIR RELATION TO THE CONCENTRATION OF CHOLESTEROL IN THE BLOOD.

Age Groups (Years)	Number of Subjects	Daily Intake of Protein (Grams)		Daily Intake of Fat (Grams)		Total Cholesterol (mg.%)	
		Mean	$s_{\bar{x}}$	Mean	$s_{\bar{x}}$	Mean	$s_{\bar{x}}$
30-39	10	65.2	7.9	98.7	15.2	176	24.6
40-49	16	58.8	7.9	87.6	18.3	190	49.3
50-59	13	51.5	6.8	81.3	17.7	219	36.6
60-69	6	58.4	8.9	65.0	26.6	250	35.6
70-79	8	45.0	9.2	62.6	18.1	251	45.4
80-90	1	59.0	.....	68.1	.....	154	.....
Mean Values for All Ages		56.1	10.0	81.6	21.7	209	48.3

Standard Partial Regression Coefficients of Concentration of Total Cholesterol in Serum.

Regression on Age	+ 0.3604
Regression on Daily Intake of Protein	— 0.2684
Regression on Daily Intake of Fat	+ 0.0326
	n = 54
	$R^2 = 0.2745$
	$(r \text{ Cholesterol-Age})^2 = 0.2244$

of these factors on cholesterol content of blood. There is a marked difference in the mean quantity of protein consumed daily by the women in the fourth decade of life and those in the eighth. In the intervening years consumption of the nutrient fluctuates around an intermediate value. On the other hand, the amount of fat ingested declines successively from decade to decade. These dietary constituents, however, apparently exert little influence on the concentration of cholesterol in the blood. The similarity in the values for R^2 and r^2 indicate that most of the variation in cholesterol which has been accounted for is attributable to age. Dietary protein and fat explain a negligible amount of the remaining variation.

DISCUSSION

For women in any age group, values for blood cholesterol spread over a considerable range. The same has been noted for men (9). Mühlbock and Kaufmann (13) have reported mean cholesterol values for a group of German women that ranged from 200 mg. per cent in the 20 to 29 year decade to 260 mg.

per cent in the 60 to 69 decade. The effect of age on concentration of serum cholesterol has been observed by other workers also (10, 11). In general, trends are the same as those reported for men (see fig. 2).

The investigation reported by Keys (7) is of particular interest in relation to the present investigation because it is based on 1492 midwestern men whose patterns of food intake probably are more or less comparable to those of the women herein studied. Comparison of the curves in figure 2 representing these two groups suggests that the maximal cholesterol concentration in the serum appears a decade later in life in women than it does in men. The data reported by Kountz and associates (11) also support this observation.

The cholesterol-age trend has been demonstrated also in longitudinal studies in which several individuals were re-observed after an interval of time had elapsed. For example, Sperry and Webb (16) reported the influence of aging on serum cholesterol by re-examination of some 22 individuals, 14 men and 8 women, fourteen years after the first observation was made. A rise in the concentration of serum cholesterol of 22.7 per cent occurred in women whose mean age at the time of the first test was close to 31 years. This increase corresponds to increments noted in the present cross-sectional study relating to Iowa and Nebraska women as shown by a comparison of the mean concentrations of serum cholesterol, as estimated from figure 1, for women aged 30 and for subjects aged 44. There is a difference of 18 per cent between these two age-groups.

Keys and his coworkers have discussed the reversal in the cholesterol-age trend that oc-

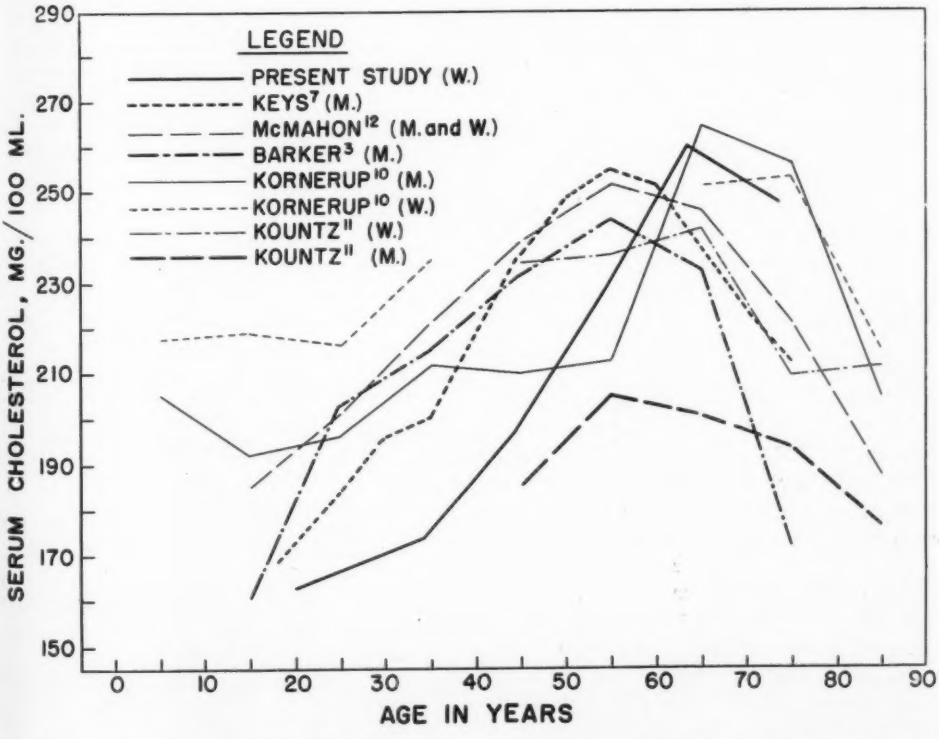

FIG. 2. Mean concentration of total cholesterol in the serum of healthy men (M.) and women (W.).

curs at about age 50 in men, and which has also been observed in the present study of women at about age 60. A fall in the concentration of serum cholesterol does not mean necessarily that the amount of the constituent in the blood declines with age. Instead, decreased concentrations noted in older people may be values characteristic of survivors. It has been suggested also that the change in the cholesterol trend after age 50 or 60 does not need to be explained in terms of selective mortality. It may depict rather the "ordinary ontogeny of the healthy individual man" (7, 9).

It presently is believed that blood cholesterol has its origin in some of the short chain compounds arising in the metabolism of fats, carbohydrates, and protein (2, 4, 5). There is convincing evidence that dietary fat plays an important role in determining the level of cholesterol concentration in the blood (1). Keys (8) on the basis of dietary studies made in England, Naples and Madrid recently has observed large differences in the serum cholesterol levels in different population groups. He believes that after age 20 dietary practices exert a marked influence on the cholesterol metabolism and that habitual food patterns characterized by the use of large amounts of fat and by abundant or excessive calories are associated with concentrations of serum cholesterol that tend to rise progressively with age until "mode of life and/or the aging process itself forces a change."

No evidence, however, was collected in the present investigation that indicates that fat accounts to any appreciable extent for the variations observed in serum cholesterol concentrations of the women studied. Generous amounts of fat were eaten daily. Fat contents of the diets, as calcuated from weighed food intakes, ranged from 99 to 63 Gm. per day and provided from 43 to 36 per cent of the total energy value. These women thus were habituated to the use of relatively large amounts of fat. Differences in intake by the subjects in any age-group probably were not great enough to be reflected in differences in serum cholesterol levels. The possibility, however, cannot be ignored that intakes of fat of the order ingested by these women, particularly those representative of the 30, 40, and 50 age-decades, contributed to the increments in cholesterol concentrations observed with advancing age.

There seems to be ample evidence that food cholesterol exerts no influence on the concentration of the constituent in the blood (6). For this reason, no study was made of the intake of cholesterol by the women in this study.

Summary

The concentration of total cholesterol in blood serum has been determined in 184 healthy mid-western women, ranging in age from 18 to 92 years. The mean serum total cholesterol value for this group was 209 ± 48.2 mg. per cent. A significant relationship existed between the concentration of serum cholesterol and the age of these subjects. The cholesterol content of the serum increased progressively from 163 mg. per cent for the women in the 30-year-decade to a maximal value of 260 mg. per cent for the women in the 60-year-decade. Thereafter, the concentration of the cholesterol constituent declined.

In this study, body weight, basal metabolic rate, diastolic blood pressure, and dietary intakes of protein and fat did not seem to bear significant relationships to the concentration of total cholesterol in the blood.

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THE RELATIONSHIP BETWEEN CRITICAL FLICKER FREQUENCY AND CHRONOLOGIC AGE FOR VARYING LEVELS OF STIMULUS BRIGHTNESS

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MOST age curves for sensory and motor functions are characterized by a slow decline in scores or capacities during maturity and old age. Critical flicker frequency (CFF), i. e., the lowest rate of stimulus intermittency required to produce a sensation of uniform illumination, also seems to be influenced by the age of the observer. A number of studies (1, 3, 5, 6, 7) have been conducted which show that fusion thresholds for subjects of advanced age tend to be lower than for young adults, but the relatively small samples and the limited age ranges have made it difficult to apply their results to a better understanding of the form of the relationship between CFF and age, or to relate it to the decrement in age curves for other psychophysical measurements.

The purpose of this research was to investigate the relationship between foveal CFF and chronologic age at different levels of stimulus brightness. Specifically it was designed to answer the following questions: 1) What is the functional relationship between foveal CFF and age? Are the parameters of this relationship the same for different levels of stimulus brightness? 2) Is the value of the slope of the foveal CFF-log brightness curve the same for different age groups?

MATERIAL AND METHOD

The subjects were 120 white men, ranging in age from 20 through 79 years. They were selected from the patient population of two hospitals and were equally divided, by decades, into 6 age-groups. Patients with cardiovascular disturbances, diseases of the central nervous system, a history of optical surgery, or gross visual defects were excluded. Seventy-six subjects were patients from the medical services who were about ready for discharge, or were orthopedic or pre-operative elective surgery cases. The remaining 44 subjects were members in a domiciliary home and were relatively healthy.

The stimulus light was produced by an episcotister with a 1:1 light-dark ratio. The light system was operated on direct current and the rate of intermittency was controlled by means of a variable resistor. The stimulus field was a square of diffused constant light in the center of which was a circle of intermittent light. The total stimulus field subtended a visual angle of 1 degree, 56 min.; the intermittent stimulus field, 44 min. Thus foveal stimulation was assured when the stimulus field was centrally fixated.

Binocular foveal CFF for each of the 120 subjects was determined at 3 levels of stimulus brightness: 0.0912 millilamberts, 0.5388 millilamberts, and 1.7420 millilamberts. Henceforth these values will be referred to as levels 1, 2, and 3 respectively. CFF was defined as the average of 4 ascending (flicker to fusion) and 4 descending (fusion to flicker) judgments.

The results of a preliminary study indicated that these 3 levels of brightness, which are approximately the same distance apart on a log millilambert scale, would yield CFF values which would fall on the straight line portion of the CFF-log I curve as devised by Hecht and Verrijp (2).

After a 10-minute dark adaptation period

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the observer was given 20 practice trials at level 1. The readings were begun at the lowest level of brightness and terminated at the highest level in a non-randomized manner. A rest period of two minutes was allowed before the readings at the next higher level were made.

Results and Discussion

An inspection of table 1 shows that there are differences in mean CFF for all age-groups, and that the mean values of CFF tend to decrease with increased age for each of the 3 experimental conditions. These mean CFF's are averages of the 20 individual CFF's within a given age-group. Variability does not increase with increased age, but it tends to be greater for all age-groups when the level of brightness is increased.

In figure 1 these mean CFF's have been plotted against chronologic age and the relationship between them found to be linear and negative for each of the conditions of brightness. The calculated values of the slopes of these 3 age curves, as determined by the method of least squares, are −.1110, −.1631, and −.1796, respectively.

Pearson r's, based on the entire sample of 120 cases, were calculated to determine the relationship between CFF and chronologic age. In each of the 3 conditions it was found to be −.74.

These data in table 1 and fig. 1 indicate that the decrement in CFF for observers above 20 years of age is similar in form to the decrement in age curves for other sensory and motor functions (4). It is evident from the gradual decrease in mean CFF for succeeding decades and the range of CFF within any given age-group that this visual function has all of the characteristics of what has been described as the decrement in typical age

Table 1. Means, Standard Deviations, and Ranges of CFF (In Cycles per Second) for 6 Groups, at 3 Levels of Stimulus Brightness.

Age-Group (Years)		Brightness Levels		
		No. 1	No. 2	No. 3
20–29	Mean	18.00	32.33	40.75
	S.D.	1.67	2.06	2.28
	Range	15.2–22.0	28.2–37.3	36.7–46.7
30–39	Mean	17.31	30.90	39.05
	S.D.	1.19	1.55	1.86
	Range	15.8–20.9	27.6–33.8	35.1–41.8
40–49	Mean	16.36	29.51	37.03
	S.D.	1.63	2.41	3.07
	Range	11.7–18.7	23.2–32.7	29.4–41.3
50–59	Mean	15.23	28.17	35.40
	S.D.	1.79	2.51	2.67
	Range	12.3–20.4	22.5–33.3	30.5–42.3
60–69	Mean	14.32	27.53	35.20
	S.D.	1.66	2.46	2.37
	Range	11.3–16.9	23.2–32.7	30.5–40.2
70–79	Mean	12.72	23.95	31.64
	S.D.	1.75	2.65	3.23
	Range	9.5–15.8	19.3–28.2	25.3–36.1

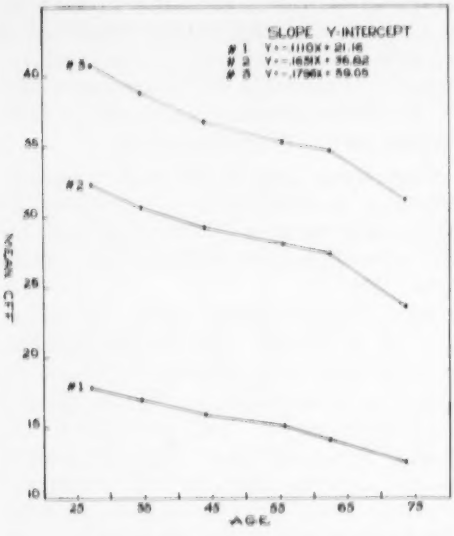

FIG. 1. Critical flicker frequency as a function of chronologic age, for 3 levels of stimulus brightness. Each point represents the mean of 20 CFF values and the mean chronologic age for age-groups divided in decades from 20 through 79 years. The straight line equation, $Y = bX + a$, was fitted to these data, and the values of its constants a and b, are in the upper right of the graph.

curves for other psychophysic measurements. The relatively high negative correlation ($-.74$) of CFF with age indicates that this visual function is more associated with chronologic age than are some other types of sensory and motor functions. Many of these skills are markedly influenced by the past experience of the subject. Such does not seem to be case with CFF.

The analysis of variance technique for repeated measurements on the same subject, and the t test were utilized in determining the statistical significance of these results.

The between-subject differences are significant beyond the 1 per cent level of confidence for each of the 3 conditions. These individual differences are not unexpected; of more immediate concern is the fact that when these individual values are divided into age-groups, the differences between the mean CFF values for that age group are also significant beyond the 1 per cent level of confidence.

At levels 1 and 3 the mean CFF for groups above 70 years is lower than the means for groups below 40 years. At level 2 the mean CFF for the oldest group is also significantly lower than the means for groups below 50 years of age. No other differences are significant. These findings indicate that although there is consistent trend toward lower CFF with increased age the difference does not become significant until extremely late in life.

The variations in reported age at which CFF becomes significantly lower may be attributed, in many instances, to inadequate Ns and limited age-ranges, but the extreme differences in the physical properties of their stimulus light, especially its intensity, is also influencing the magnitude of the threshold difference between age-groups. This dependency on stimulus brightness can be seen in the increased value of the CFF-age curves at level 3. Recall that the value of the slope at the highest level of brightness was $-.1796$ as compared to a value of $-.1110$ at the lower level. It can also be detected in the magnitude of the differences between the youngest and the oldest age groups. At level 1 the mean CFF for the 20 year group is 5.28 cycles per second higher than the mean for the 70-year group. At level 2 it is 8.34 cps. higher while at level 3 the differences between the means has increased to 9.11 cps. This age decrement dependency on stimulus brightness reveals itself even more vividly when age is considered as a variable in the CFF-log brightness relationship.

As stated earlier, the 3 levels of brightness were selected because they would yield CFF values which would fall near the lower, middle, and upper end of the straight-line portion of the CFF-log I curve. Since measurements were made on each subject at each of these 3 levels, the straight line equation can be fitted to these data and the constants of the curves evaluated for differences.

Using a simple analysis of variance technique to evaluate the age group differences of these slopes an F-ratio of 8.784 was obtained which is significant beyond the 1 per cent level of confidence.

TABLE 2. THE MATRICES OF t-VALUES FOR AGE DIFFERENCES IN CFF AT 3 LEVELS OF STIMULUS BRIGHTNESS.*

Age-Group (Years)	20–29 Years	30–39 Years	40–49 Years	50–59 Years	60–69 Years
30–39	.5062				
40–49	1.1682	.6620			
50–59	1.9470	1.4080	.7788		
60–69	2.5312	2.0249	1.3629	.5841	
70–79	3.6215†	3.1152†	2.4533	1.6744	1.0900
Age-Group	**20–29 Years**	**30–39 Years**	**40–49 Years**	**50–59 Years**	**60–69 Years**
30–39	.7010				
40–49	1.3211	.6201			
50–59	1.9951	1.2941	.6740		
60–69	2.2917	1.5907	.9706	.2966	
70–79	3.9902†	3.3893†	2.6691†	1.9951	1.6986
Age-Group	**20–29 Years**	**30–39 Years**	**40–49 Years**	**50–59 Years**	**60–69 Years**
30–39	.6825				
40–49	1.5533	.8708			
50–59	2.2123	1.5298	.6590		
60–69	2.3299	1.6474	.7766	.1177	
70–79	3.7891†	3.1066†	2.2358	1.5768	1.4592

* Since the standard error of the difference is based on 114 degrees of freedom, the t-values are considered as critical ratios.

† Significant beyond the 1 per cent level of confidence.

TABLE 3. THE MATRIX OF t-VALUES FOR AGE-GROUP DIFFERENCES IN THE VALUE OF THE SLOPE OF THE CFF-LOG ILLUMINATION CURVE*

Age-Group (Years)	20–29 Years	30–39 Years	40–49 Years	50–59 Years	60–69 Years
30–39	1.4823				
40–49	3.1416†	1.6593			
50–59	3.8495†	2.3672	.7080		
60–69	2.9424†	1.4602	.1991	.9071	
70–79	6.1504†	4.6681†	3.0088†	2.3009	3.3080†

* Since the standard error of the difference is based on 114 degrees of freedom, the t-values are considered as critical ratios.

† Significant beyond the 1 per cent level of confidence.

The t test was again utilized to determine which of the age group differences are significant.

The mean value for the 20-year group is significantly higher than the means for the groups from 40 through 79 years. The means for the 20 through 50 year groups are all significantly higher than the means for the oldest group. No other differences are significant. These results indicate that, although CFF varies directly with the log of the brightness, the rate of acceleration is slower in the older age groups. In fact, the values of the CFF-log brightness curves seem to be more sensitive to age changes than is CFF alone. Significantly lower CFF's did not appear until after 70 years of age, whereas the values of the CFF-log brightness curves becomes statistically lower in observers above 40 years of age.

Summary

The following general conclusions may be drawn from the results of this study:

1. The functional relationship between foveal CFF and age is linear and negative. The form of this relationship has all of the characteristics of the decrement in age curves for other sensory and motor functions.

2. The parameters of the CFF-age curves are altered by changes in the level of stimulus brightness. The rate of decay of the slope is increased when the level of stimulus brightness is increased.

3. Although mean CFF consistently decreases for groups above 20 years of age, this decrement is statistically significant only for groups above 70 years of age.

4. The slopes of the foveal CFF-log brightness curves are less accelerated in older subjects. These differences and the variations in the slopes of the CFF-age curves at different levels of brightness show that the same increment of brightness yields a smaller increment of CFF for subjects in older age groups. It adds further evidence that the extent of the age decline in CFF is dependent upon the level of brightness at which the measurements are made.

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ELECTROENCEPHALOGRAPHY AS A DIAGNOSTIC AND PROGNOSTIC AID IN STUDYING THE SENESCENT INDIVIDUAL
A PRELIMINARY REPORT

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In January, 1952, a geriatrics project was begun at the Napa State Hospital having as its primary aim the refinement of techniques used in the diagnosis of brain syndromes occurring in advanced age groups. Of the several methods of approach being employed in this program, electroencephalography constitutes an aspect of the study that may, according to findings to date, prove to be of considerable significance in the ultimate achievements of the project. In using electroencephalography as an adjunct to other diagnostic procedures, it is hoped that electroencephalographic criteria may be established that will be useful in differentiating various types of psychoses observed in the senium.

Electroencephalographic studies in this program are also being considered from the standpoint of determining which electroencephalographic findings may be of prognostic value in selecting individuals who are suitable for rehabilitation from among persons with mental illnesses occurring in advanced age who have been admitted to state hospitals. A review of the literature indicates that most of the studies investigating brain waves in senescent persons have been directed toward establishing the characteristic features of a single tracing and the correlation of these features with the clinical condition at the time of the recording. This study, in contrast to others, is more concerned with changes observed in serial recordings on single individuals than with the basic features of single recordings.

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Method and Technique

In selecting case material for this study, all male patients above the age of 55 who are clinically considered to have chronic brain syndromes of arteriosclerotic or senile origin, are alternately assigned to a study or a control group as soon after admission to the hospital as a tentative clinical diagnosis can be made. The study group resides on a single ward and is offered intensive rehabilitation therapy. "Control" patients are dispersed on various wards and receive routine ward care. For electroencephalographic studies only, apart from the over-all project, serial records are being taken on mentally normal controls above the age of 55; these individuals are either state employees or residents of a nearby veterans' home. Electroencephalographic records are repeated every three months, or more often when electroencephalographic findings or clinical symptoms suggest an indication for more frequent examination.

For this study an 8 channel Edin machine, Model 400A, is being used. Scalp to ear recordings are made from needle electrodes placed in the frontal, parietal, mid-temporal, and occipital areas, and hyperventilation recordings are made routinely on those who are well enough to comprehend instructions. Special techniques are used only when electroencephalographic changes suggest unusual pathology or when clinical signs warrant detailed investigations. These techniques include scalp to scalp recordings, metrazol stimulation recordings, 16 lead localizing recordings, and sleep recordings.

During the first two years of study, a total of 347 records have been taken on 147 individuals; 46 of these tracings are single recordings and 301 are serial recordings on 101 individuals. The number of serial recordings on a single individual varies from 2 to 8. This number is determined by two factors, the duration of hospitalization and the presence of an indication for recordings to be made at more frequent intervals than every three months.

In this preliminary report, precise figures have been converted to approximate percentages as records have not yet been accumulated in sufficient quantity to have statistical significance.

Dominant Electroencephalographic Features

At this stage of the study, the features of the electroencephalograms that merit greatest consideration include dominant rhythm, focal activity, and paroxysmal dysrythmia.

Dominant Rhythm.—The common finding that has been consistently observed in a high percentage of persons in the senescent period is a slowing in dominant rhythm. This phenomenon of slowing below 8 cycles per second is considered by Cohn (1) to be definite evidence of disturbance in brain physiology, and occurs according to the neurophysiologic condition of the brain regardless of the chronologic age of the individual. Gibbs and Gibbs (3) consider large slow waves in the frontal areas as being normal in persons past 50. Although it may be suitable to alter the standards of abnormality in reading routine electroencephalograms on elderly individuals as suggested by Silverman and associates (9), for research purposes in this study the conventional standards are followed, and all records containing significant quantities of activity below 8 cycles per second are classified as abnormal.

Slowing frequently appears in these records as the only evidence of abnormality, although Mundy-Castle (8) reports that most of the senescent individuals in his series who showed theta activity had electroencephalograms which were abnormal in other respects. Abnormal slowing in the dominant rhythm below 8 cycles per second has been observed in about 60 per cent of patients who require continued hospitalization or who have subsequently died. Among normal controls and patients who have gone on leave of absence, abnormal slowing appears in only about 25 per cent.

Most of the individuals in this study who have a dominant alpha rhythm show alpha activity of 8 cycles per second which is in the lower range of normal and is slower than the average alpha rhythm noted in younger age groups. Alpha rhythm of faster than 10 cycles per second has been noted very infrequently in any of these groups, which is in keeping with the findings of Davis (2). Davis (2) has reported that the alpha index in older persons is not susceptible to influences that may affect alpha activity in younger individuals and that the decrease in alpha index is permanent. Not infrequently in this series, however, the alpha organization and amplitude are observed to improve with hyperventilation and occasionally the basic rhythm increases in rate. More than one-fourth of the currently hospitalized patients have shown an increase in rate of the basic rhythm, indicating that it is a more labile factor than had been realized. A smaller number of patients have shown a progressive slowing of basic rhythm.

Increase in the basic frequency from one recording to the next appears more often in slow records than in records having a dominant rhythm within the normal range. Of 19 deceased patients who had serial records taken, 7 show no change in frequency, 7 show progressive decrease in frequency, 4 show improvement in basic rhythm in the last record taken prior to death, and 1 series shows increase in frequency with, subsequently, decrease in frequency appearing in the final record. Of the 7 series showing diminution in frequency, 3 show decrease from a normal to a slow range, 2 show decrease within an abnormally slow range, 1

shows decrease in a normal alpha range, and 1 shows decrease from a normal to a slow range in occipital rhythm only, rhythm remaining the same in other leads. Of the 4 series showing increase in frequency 2 show increase in frequency from a slow to a normal range and 2 show increase in frequency remaining in an abnormally slow range.

Focal Activity.—In this study there has not been noted the large percentage of temporal foci that Silverman (9) has observed in his series of psychologically testable individuals past 60. In the small series of records on 22 normal controls and patients who have been well enough to go on leave of absence that are included in this study, focal abnormality has appeared in only one individual, and this consists of bilateral frontal slowing.

Foci observed in the records of hospitalized or subsequently deceased patients have been scattered with no distinct trend to preponderance in one area except that bilateral frontal slowing and combined temporal and parietal slowing in either the right or the left hemisphere appear somewhat more frequently than focal activity in other areas. On patients who have died, all of the records containing focal activity have also shown generalized slowing. Among currently hospitalized patients, almost half of the records containing focal activity show a normal basic alpha rhythm of 8 to 9 cycles per second. It is of interest to note that among hospital patients who have survived for as long as 6 months after need for hospitalization, the incidence of generalized slowing is lower in records containing focal activity than in those records having no focal abnormality.

Focal activity among serial records on individuals has been surprisingly variable and changes noted in focal signs include improvement, recovery, and exaggeration, as well as diffusion to involve adjoining areas or an entire hemisphere, constriction to a more limited area, or appearance of new foci. Asymmetry, or difference in amplitude with little difference in frequency or wave-form between homologous leads, has been frequently noted to occur in areas that have previously or subsequently shown focal activity. Serial records suggest that in the senile individual asymmetry is probably more likely to be related to focal abnormality than to the causes of asymmetry in younger persons; Cohn (1) considers asymmetry generally to be related to cerebral dominance and this possible relationship cannot be disregarded in the senile brain wave.

Paroxysmal Dysrythmia.—Apart from generalized slowing and focal abnormality, these studies tend to indicate that paroxysmal activity is related to the duration and inversely to severity of the pathologic condition. Paroxysmal activity appears in over 40 per cent of currently hospitalized patients, and the incidence of generalized slowing is considerably lower in those records that contain paroxysmal activity. Of 31 individuals showing paroxysmal activity, only 10 show basic slowing below 8 cycles per second, an incidence of 30 per cent, where slowing appears in 60 per cent of this group of records taken as a whole. Although electro-convulsive therapy has been given to several patients in the hospital group, the only patient having paroxysmal activity who received electroconvulsive therapy showed a non-paroxysmal record following therapy. Of 48 patients who have died, 7 have shown paroxysmal activity, but 2 of the 7 patients had no paroxysmal activity in the last record taken prior to death. The incidence of paroxysmal activity in the 48 patients who have died is about 10 per cent, or about one-fourth the incidence noted in patients having a longer survival period.

Correlations

In the original formulation of this geriatrics project, it was planned to correlate electroencephalographic findings with postmortem findings and clinical symptomatology, including the degree of intellectual deterioration, clinical neurologic signs, progress in the hospital, and clinical diagnosis.

As the study progresses, there becomes apparent a need for further correlations so that new facets may be introduced from time to time as new findings appear. No statistical correlations have been completed but the following comments may be made regarding comparisons:

Clinical Symptomatology.—In correlating electroencephalographic findings with clinical symptomatology electroencephalographic changes are compared with changes noted in the hospital adjustment scale as devised by McReynolds and Ferguson (7), and, corroborating the observations of Hoch and Kubis (4), McAdams (6), and Luce and Rothschild (5), it seems that the correlation will be close. Electroencephalographic changes have variably appeared either prior to or subsequent to significant changes in the hospital adjustment scale; this finding has been too inconsistent to warrant a definite conclusion at this time. Electroencephalographic findings have not been correlated with psychologic test data as many of the subjects are not testable; however, the hospital patients are seen by a psychologist and tested when possible so there will be adequate material for psychologic correlations as the study proceeds. This group of testable hospitalized patients will be more comparable to Silverman's (9) series of testable individuals past 60 than is the presently reported series.

Autopsy Findings.—Readable electroencephalograms have been taken on 47 patients who have died, and autopsies were obtained on 17 of these patients. Of the 17 having autopsies, only 7 had survived long enough for serial records. A long period of study will be necessary before there can be accumulated a significant number of electroencephalograms to correlate with pathologic findings. However, observations on 14 patients on whom pathologic reports are available are reported in table 1.

The following comments regarding clinical findings, postmortem diagnoses, and electroencephalographic changes may serve to illustrate individual points of interest in these cases:

Patients No. 1, 4, and 13 showed focal activity on electroencephalography that is not explained on autopsy. Patient No. 1 was relatively intact intellectually and his mental condition was reported to be improving as his electroencephalogram improved prior to death due to carcinomatosis. Autopsy findings do not explain the focal activity present at a time when the patient was more confused than at the time of a subsequent normal recording.

Patient No. 2 showed a normal and improving electroencephalogram despite the pathologic diagnosis of Pick's Disease. Clinically, this patient had a Parkinson-like tremor with autopsy findings of involvement of the extrapyramidal nuclei. One might speculate that this patient had a relatively intact cortex although his clinical progress was that of progressive deterioration.

Patient No. 3 had frontal lobe symptoms that were progressive over a period of five years prior to state hospitalization. The normal electroencephalogram in the presence of a very large meningioma is difficult to explain except on the basis of a gradual compensatory process in a person who had premorbidly been an emotionally stable college professor. This patient showed little deterioration in intellectual processes.

Patients No. 5, 7, 9, 10, and 11, are the 5 instances in this series of 14 in which the clinical, electroencephalographic, and pathologic findings all correlated closely. All of these patients showed slow EEG's, were markedly deteriorated intellectually, and had moderate to severe pathologic conditions of the brain of senile or mixed senile and arteriosclerotic type.

Patient No. 6 is of interest in that the second EEG was abnormally slow although the patient was mentally distinctly improved over his condition at the time of an initial normal record. The abnormally slow record preceded by three weeks the occurrence of a cerebro-vascular accident and one might speculate that the abnormal EEG might have occurred concommittantly with physiopathologic changes preceding a vascular

TABLE 1. CORRELATION OF PATHOLOGIC AND ELECTROENCEPHALOGRAPHIC OBSERVATIONS.

Pathologic Findings	Hospital Adjustment Scale[1]	Electroencephalographic Findings
1. No brain pathology	None	EEG No. 1 Mixed fast and slow record; focus, right parietal area
	68%	EEG No. 2 Normal record, some 10 cycle per second alpha activity
2. Pick's disease	29%	EEG No. 1 Normal EEG
	3%	EEG No. 2 Normal EEG, improved in organization
3. Frontal meningioma	None	EEG No. 1 Normal EEG
4. Mixed senile and arteriosclerotic brain disease, no evidence of focal pathology.	None	EEG No. 1 Slow record focus, left temporal area
5. Mixed senile and arteriosclerotic brain disease	26%	EEG No. 1 Slow record
6. Senile brain disease, acute infarction, left temporal lobe	41%	EEG No. 1 Normal EEG
	65%	EEG No. 2 Mildly slow EEG
Stupor	None	EEG No. 3 Very slow, high amplitude, diffusely abnormal
	None	EEG No. 4 Slow high amplitude, left hemisphere lateralization
	None	EEG No. 5 Same as EEG No. 4
	None	EEG No. 6 Slow high amplitude record; focus, left temporal area
7. Senile brain disease	43%	EEG No. 1 Slow record
8. Senile brain disease	99%	EEG No. 1 Mild paroxysmal dysrythmia, record otherwise normal
9. Senile brain disease, gross atrophy, frontal lobes	None	EEG No. 1 Slow record, bilateral frontal focus
10. Senile brain disease	50%	EEG No. 1 Slow EEG
11. Senile brain disease, gross atrophy, left temporal and both occipital lobes	21%	EEG No. 1 Slow EEG, focus left temporal lead, questionable focus left parietal
12. Arteriosclerotic brain disease, right subdural hematoma; infarction, right parietal lobe	47%	EEG No. 1 Slow record, focus right parietal. EEG No. 2 Slow record, focus right occipital, record shows disintegration, abnormality more diffuse
13. Arteriosclerotic brain disease, no evidence of focal pathology	46%	EEG No. 1 Slow EEG, focus left occipital, left hemisphere lateralization. EEG No. 2 Slow EEG, no focus, slower and more disintegrated.
14. Arteriosclerotic brain disease	None	EEG No. 1 Normal EEG

[1] According to estimates of clinical behavior, those having a Hospital Adjustment Scale score above 60 per cent generally seem to be relatively intact intellectually and a change of 10 per cent in Hospital Adjustment Scale is usually accompanied by obvious changes in mental condition.

accident but without reflection in clinical condition.

Patients No. 8 and 14 are of interest in that the EEG findings correlate with the clinical status of the patients but pathologic findings are at variance. Both of the patients were rather well preserved intellectually and had normal EEG's except for mild paroxysmal activity in one, yet both showed moderately severe pathologic conditions.

Patient No. 12 showed in an initial record a right parietal focus and in a second record no parietal focus, but focal activity appeared in the right occipital area. On autopsy an infarction of the right parietal lobe was found. This series effectively illustrates the problem of fallacious impressions resulting from routine electroencephalographic classification systems or incomplete reporting of EEG findings. One might readily assume on superficial examination of EEG reports in this case that there had been recovery from parietal focal activity and a shift of focus to the occipital area. However, the general disintegration in the second record and increase in diffuse abnormality leads one to speculate that the initial focal abnormality in the parietal area did not improve but became diffuse to involve all areas except for sparing one occipital area.

Pre-morbid Personality.—As knowledge of the relationship between electroencephalography and personality increases, it may be a matter of interest to study the relationship between personality and the senile brain wave. Is a strong occipital alpha activity evidence of personality type, is this a residual of a once good brain wave, or is this a favorable sign indicating a degree of cortical intactness? Is a low-voltage fast record the record of an anxious person who is aging, is it suggestive of retained alertness, or is it indicative of increasing anxiety with senility? No conclusion has been reached regarding the relationship between pre-morbid personality and senile brain wave characteristics. Very occasional records show superior organization in the parietal or temporal leads, and this leads one to speculate that brain wave organization may disintegrate in a pattern that is the reverse of improving organization observed in infancy. Situational stress as a contributory or precipitating factor necessitating hospitalization is considered from the standpoint of sociologic, clinical, and electroencephalographic findings.

Duration of Illness.—As this study progresses, electroencephalographic findings will be correlated with duration of illness, type of onset, and length of survival in the hospital. Careful medical and social histories are being obtained from relatives when possible, and this information is being evaluated for correlation.

Conditions Other Than Senile or Arteriosclerotic Brain Disease.—Records are being acquired for future reference on patients having organic brain disease which is known to have certain reversible or irreversible qualities such as general paresis, Korsakoff's psychosis, Alzheimer's disease, and Pick's disease. In these records, there may be found verification of findings that suggest permanent rather than recoverable changes, or vice versa. Other records on patients over 55 that have been requested on the basis of suspected cerebral disease will be correlated when autopsy reports are available. Through this correlation, more may be learned about the responsiveness of the senile cortex apart from findings that are associated with cerebral arteriosclerosis and senile brain disease. Records on patients receiving electro-convulsive therapy will be considered as a group to be compared with records on younger patients receiving electro-convulsive therapy in order to determine if one may anticipate comparable brain wave changes in young and elderly patients as a result of this therapy. Is the cortex past 50 able to reflect in the brain wave the same abnormality that a younger cortex would show with a similar irritative or degenerative process? Does the aging cortex respond in a comparable but less vigorous fashion than the youthful cortex, or may a certain response have a different significance in the senile brain?

Hyperventilation Responses.—No consist-

ent trend in hyperventilation response appears, but a greater diversity of responses has been obtained than was anticipated. As in younger individuals hyperventilation responses include slowing or increase in the basic rhythm, increase in severity of focal activity, change in general organization, and increase in quality or amount of paroxysmal activity. Hyperventilation response shows marked variability from one record to the next in the same individual.

Summary

As part of a long range project for studying geriatric patients in a state mental hospital, a preliminary report is presented on 347 electroencephalograms taken on 147 individuals over a period of two years.

The most impressive finding at the termination of the first two years of this study is the observation that it is exceptional for serial recordings taken on one individual at three-month intervals to remain unchanged. These changes consist of increase or decrease in the basic alpha rhythm; change in general integration; change in amount of slow activity; presence or absence of paroxysmal dysrythmia; change in symmetry; variation in hyperventilation response; and change in location, quantity, and quality of focal activity. Paroxysmal activity has been observed in normal and improving individuals over 55 and often occurs in records having a normal basic rhythm, suggesting that paroxysmal activity is indicative of a certain degree of cortical intactness and that there is an inverse relationship between paroxysmal and slow activity. Normal alpha activity is more likely to be associated with a good prognosis than is slow activity. However, predominantly slow activity is compatible with good intellectual preservation. Focal activity occurs with or without organic deterioration and may be noted in records that are either normal or abnormal in other respects. Among patients having a longer survival period, the basic alpha rhythm is normal in a greater percentage of records that contain focal activity than in those that lack focal abnormality, but this is not true of records taken on more acutely ill patients who die soon after admission, as records on these patients that show focal abnormality all have slow basic rhythms. These serial records show that increase in basic frequency occurs more often than diminution in basic frequency, which is a reversal of the findings that were anticipated prior to the study.

If electroencephalography is to prove of value in differential diagnosis of senile and arteriosclerotic brain disease, it probably will not be sufficient to consider the mere presence or absence of focal or slow activity, but rather, consideration must be given to slow wave characteristics, record organization, location of foci, and changes in the course of serial recordings.

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DERANGED CHOLESTEROL METABOLISM AND ITS POSSIBLE RELATIONSHIP TO HUMAN ATHEROSCLEROSIS: A REVIEW

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THE search today for means by which the course of human atherosclerosis may be altered has become so intensified and narrowed toward an immediate fulfillment of the researcher's desire for therapeutic success that large areas of unexplored but fundamental physiologic dynamics have been neglected. Thus, for example, scores of substances have been administered to the atherosclerotic rabbit, dog, and chicken in an attempt to inhibit the atherosclerotic process without sufficient attention being allotted to the study of the essential mechanisms responsible for the hypercholesteremia which admittedly causes the atherosclerosis. Again various steroid moieties of the blood of both patient and experimental animal have been exhaustively studied by spectrophotometric, cataphoretic, ultracentrifugal, chromatographic, and other means, although the actual source and eventual fate of these same blood lipids were not definitely known nor even seriously inquired about until recently. Such omissions sometimes have not been harmless because many of the studies which were guided and concluded by means of specialized apparatus have yielded data which in the absence of proper physiologic perspective have allowed the erection of concepts whose vertical extensions are far greater than their bases will support. Certainly, no amount of technologic refinement employed in a study of a part guarantees an essential understanding of even the contours of the whole.

It therefore seems appropriate at this time to survey the field of cholesterol metabolism and the possible relationship of its derangement to the pathogenesis of atherosclerosis. There will be a purposeful attempt to avoid emphasizing any particular segment of the field however extensive its technologic exploitation may have been in the laboratory, lest a possible *cul-de-sac* be falsely portrayed as a major pathway. Admittedly such treatment of the total field must, by necessity, consist of only a rough sketch at best but at least its general contours and magnitude will have been delineated.

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I. Normal Metabolism of Cholesterol

Cholesterol similar to some other substances of importance to the body (e.g., glucose) is both absorbed and synthesized. The amount of cholesterol that is synthesized endogenously is, in part, inversely related to the amount of exogenous cholesterol which is absorbed (77). However, despite the amount of exogenous cholesterol absorbed, the animal never completely ceases to manufacture its own cholesterol (79, 172). If the body has two ways of obtaining cholesterol, it conversely has two by which it can rid itself of this substance, namely, by excreting it or by destroying it. Since the blood cholesterol at any given instant represents a resultant of these four phases of metabolism, an understanding of changes in blood cholesterol must be based upon a prior knowledge of these basic four processes and their interrelationships.

A. Absorption of Cholesterol

(1) Intestinal Absorption

Cholesterol is apparently absorbed from the distal half of the small intestine (34). One

of the absolute requirements for such absorption is the presence of bile (66, 160, 163, 131). The essential factor present in bile seems to be bile acid (66, 170). Fat also seems to be intimately related to the absorption of cholesterol (43, 72) apparently by acting as the emulsifying vehicle and also perhaps by supplying the fatty acids needed for the esterification of cholesterol—a process proceeding *pari passu* with absorption and requiring the presence of an esterifying enzyme either in the succus entericus or in the intestinal mucosa itself (39, 169). The bile contains such an enzyme which in most animals may be derived from the pancreas (171, 192). In the rat, however, a cholesterase must also be present in the intestinal mucosa (169) in as much as removal of the pancreas does not stop either the absorption or the esterification of the steroid (36).

From the above observations, an increase in cholesterol absorption might be expected to occur whenever an excess of cholesterol or bile acid is administered. Although definitive data concerning this point are lacking, most observers believe that the chronic feeding of excess cholesterol to man does increase its absorption. The possible effect of the ingestion of excess bile acid upon cholesterol absorption in man has not been measured but in animal studies its administration together with excess cholesterol is followed by a great increase in cholesterol absorption (66) and consequent hypercholesteremia (133, 146, 152). Moreover, it has been shown (146) that such cholate induced hypercholesteremia is independent of the separate intravascular hypercholesteremic effect of cholate.

A decrease in intestinal absorption of cholesterol is thought to occur when dietary fat is severely restricted (123). More recently the ingestion of dihydrocholesterol has been found to retard or prevent the usual hypercholesteremia occurring in the cholesterol fed bird (161) and the cholesterol-cholate fed rat (143) apparently by inhibiting the intestinal absorption of dietary cholesterol, as shown in the rat (143). Some observers (87, 137) also believe that ingestion of sitosterol similarly inhibits the absorption of cholesterol in various mammals including man, but others (144, 185) have not been able to verify such inhibition. It is possible that the concentration of the active sterol(s) varied widely in the different preparations used in these studies. Among other substances believed to inhibit intestinal absorption of cholesterol are fat extracted brain extract (93) and aluminum hydroxide (142).

(2) *Lymphatic Course of Absorbed Cholesterol*

Although it has been believed for many years that most dietary cholesterol is absorbed via the intestinal lymphatics, it was only recently shown in this laboratory (18) and later by Chaikoff and associates (39) that all absorbed cholesterol is transported via the intestinal lymphatics. Even though almost all dietary cholesterol is ingested in the free state, most of the lymph cholesterol is in the esterified form.

Lymph turns a milky white following a fatty meal and such lymph abounds in chylomicra. Recently, Page, Lewis, and Plahl (134) examined the intestinal lymph of fat and cholesterol fed dogs after centrifugation at 30,000 rpm. for one hour and observed that the fatty layer resulting at the top contained a considerable amount of cholesterol. More recently studies from this laboratory (35) have indicated that 95 per cent or more of the dietary cholesterol contained in lymph travels in the chylomicron fraction.

This latter finding must be emphasized for it indicates that it is no longer correct to assume that dietary derived cholesterol is identical with that manufactured by the animal itself because the former enters into the blood bound up with other lipids in an insoluble particle and the latter as a solute. Later in this review the possible importance of this heretofore unrealized difference will be discussed.

(3) *Fate of Absorbed Cholesterol in the Plasma*

Thus enmeshed with various lipids, the chylomicron-cholesterol enters the blood. Unlike cholesterol of endogenous origin, it is

probably acted upon by at least two separate processes, the first of which is concerned with the disappearance of the turbidity of the plasma. This has been ascribed to the heparin-"clearing" factor mechanism (5). Since the turbidity of the post alimentary plasma is dependent upon the presence of colloidal lipid particles ranging from submicroscopic to microscopic aggregates (i.e., chylomicra), "clearing" is the alteration of such aggregates with consequent solution of the lipid particles including cholesterol. The extent as well as the effectiveness of this process in making cholesterol metabolically available has yet to be totally assessed in both the experimental animal and man.

A second mechanism able to rid the blood of chylomicra and their contained cholesterol is their ingestion by the hepatic R-E cells (67). Just how important this mechanism is in the total process of removing dietary derived cholesterol is difficult to state but that it is operative in the rat, rabbit, and dog seems certain (54). Indeed, as shown by this laboratory (62), it seems quite probable that the chief cause of the rabbit's dietary induced hypercholesteremia is a relative inefficiency on the part of the R-E cells of the rabbit's liver in removing dietary derived cholesterol when the latter is fed in excess.

Whether dietary cholesterol is solubilized in the plasma itself by the clearing process or within the interior of the Kupffer cell, its ultimate fate is in the hepatic parenchymal cell. Here it is stored (66, 76) for possible later discharge as such into the blood, and to a much lesser extent, in bile or for possible conversion to cholic acid (30).

(4) *Effect of Absorption of Cholesterol on Blood Cholesterol Level*

Although there is little or no change in the blood cholesterol level of the human subject or of the experimental animal (with the exception of the rabbit and guinea pig) following a *single* feeding of excess cholesterol, there seems to be little doubt that after chronic administration of excess cholesterol and other lipids, a moderate rise of blood cholesterol occurs in man (124, 175). Conversely, complete removal of cholesterol and fat from the diet *gradually* lowers the blood cholesterol of man but rarely more than 30 per cent (100).

B. *Synthesis of Cholesterol*

(1) *Predominant Role of Liver in the Synthesis of Plasma Cholesterol*

Although almost every tissue of the body, mature cerebral and adipose tissue excepted (22), seems capable of synthesizing cholesterol (77), the liver is the organ which serves as the source of almost all endogenously derived plasma cholesterol (63). Any study then of endogenous manufacture of plasma cholesterol is for all practical purposes a study of its formation by the liver. This organ seems capable of synthesizing cholesterol from such short chain fatty acids as acetic, pyruvic, butyric, hexanoic, octanoic, and isovaleric acids (141) into various intermediate products which include acetyl-coenzyme A (101), acetoacetic acid (28), β-hydroxy-β methylglutaric acid (140), squalene (108, 176, 190), and possibly Δ^7 cholesterol and 7 dehydrocholesterol (103, 108).

There is very good evidence that the cholesterol first formed in the liver is discharged into plasma and bile in the free state (77, 86, 191). Measurement of the rate of hepatic synthesis of cholesterol is not an easy process, although tritium (19) and radioactive carbon (78) have been used for this purpose. However, the data derived from such measurements can only be considered valid if 1) the rate of destruction or conversion of cholesterol, 2) the continuous and dynamic exchange between hepatic and plasma cholesterol, 3) the prior presence of cholesterol and cholesterol precursors in the liver, 4) the possible competition for the specific radioactive precursor by other metabolic processes, and 5) the necessity for multiple sampling, are considered in the final calculations. It is obvious, however, that in the intact animal these 5 factors may be extraordinarily difficult not only to control but even to assess. Data therefore obtained from

measurements made with precursor material containing radioactive atoms may represent extremely accurate estimates of the degree of incorporation of a given atom but the physiologic inferences derived from this last are not necessarily of the same precise verity. This is a fact not too well appreciated by all workers in the field.

Besides the tracer method of measuring the hepatic rate of synthesis of cholesterol, estimates may be obtained by a simpler and more dependable technique. Bile cholesterol seems to represent under most circumstances an increment of that cholesterol newly synthesized and discharged by the liver into the blood, rather than an excretory product *per se* of the liver (32, 107).

It is thus understandable why bile never contains an increased amount of cholesterol after excess cholesterol is injected intravenously (32). This discovered significance of bile cholesterol also explains the findings of Gould and associates (78) and of Landon and Greenberg (107) who observed that, after the administration of radioactive acetate, bile cholesterol had a higher activity than the cholesterol from any other tissue in the body, including the plasma and liver. The latter tissues perhaps exhibited less activity because of the diluting effect of the inactive cholesterol present before the administration of the radioactive precursor.

Although it is probable that all or most of the bile cholesterol is newly synthesized by the liver, some of the bile cholesterol may be derived by dynamic exchange from cholesterol other than that newly synthesized. This may possibly explain the constancy of bile cholesterol secretion found in both the cholesterol starved and fed animal. In either nutritional condition, of course, the *rate* of hepatic incorporation of a tracer into cholesterol *might* possibly be different from the fixed rate of discharge of bile cholesterol. In that event, the quantity of bile cholesterol secreted would not reflect the same metabolic process as the rate of tracer incorporation.

However, Landon and Greenberg (107) have found that *all* the secretion of radioactive cholesterol into the bile occurs within six hours of the administration of radioacetate, that is, during the time in which cholesterol is being synthesized. The bile cholesterol secreted subsequently is no longer radioactive even though much radiocholesterol is still present in the liver and blood. This convincing evidence gives additional assurance that bile cholesterol is a fractional part of the cholesterol newly synthesized by the liver. Since the influence of diet is not absolutely clear, if secretion of cholesterol in bile is to be employed as a measure of the rate of its synthesis by the liver in any specific experiment, it would seem conservative practice to ensure that both the experimental and the control animal absorb the same amount of dietary cholesterol.

(2) *Factors Influencing Rate of Hepatic Synthesis of Cholesterol*

(*a*) *Ingestion of Exogenously Derived Cholesterol*—Administration of excess dietary cholesterol to the experimental animal (77, 79) results in a marked reduction in the hepatic rate of incorporation of C^{14} acetate into cholesterol. Conversely, omission of cholesterol from the diet might be expected to be followed by an increase in the rate of incorporation of C^{14} acetate. This latter study, however, has not been done.

(*b*) *Age of Animal*—Little is known about the effect of age upon the rate of endogenous synthesis of cholesterol but in the experimental animal (i.e., the rat) the rate seems to vary inversely with the age (149).

(*c*) *Injury and Disease of Liver*—Despite the frequently observed occurrence of hypercholesteremia in diseased or injured liver states, there is no evidence that this is due to a primary increase in rate of cholesterol synthesis. On the other hand, severe experimental injury of the liver of the rat either by surgery or by administration of carbon tetrachloride is followed by a decrease in rate of liver synthesis of cholesterol (32). Recently it has been suggested (181) that injury to

the liver may increase the rate of cholesterol synthesis therein. This suggestion was prompted by the observation that after administration of a labelled cholesterol precursor, a greater concentration of label in cholesterol was found in the liver which had been injured than in the control liver. This finding, however, could well be due to the relative failure of an injured liver to convert its newly synthesized, hence labelled, cholesterol into other substances (e.g., cholic acid); thus such cholesterol would accumulate, making it falsely seem that an increase in its synthesis had occurred.

The dual role of the liver in respect to the discharge into, and later removal of cholesterol from, the blood allows the possibility that the latter function could under certain conditions be more severely interfered with than the former so that although both functions might be decreased by disease or injury, a hypercholesteremia nevertheless might result.

(*d*) *Effect of Various Hormones*—In our experience (37, 145), the most powerful stimulus to increased synthesis of cholesterol by the liver has been the administration of excess thyroid hormone. Conversely, experimental production of hypothyroidism markedly decreased the rate of cholesterol synthesis. The failure of plasma cholesterol to reflect these changes by a respective rise or fall is probably due to similarly directed and even greater changes in rate of cholesterol conversion and/or destruction.

The administration of other hormones seemed (147) to have much less effect upon the rate of hepatic synthesis of cholesterol in rats. Thus, cortisone, testosterone, and progesterone had little or no effect, while estrogen seemed to depress the rate of hepatic synthesis of cholesterol. Administration of adrenocorticotrophic hormone on the other hand seemed to increase the rate of synthesis.

C. *Excretion of Cholesterol*

Significant quantities of unchanged cholesterol are lost to the body only via the feces. Since the content of cholesterol present in bile is independent of the plasma cholesterol level and seems to be dependent upon the rate of cholesterol synthesis by the liver (32), the only mechanism available to the body for the possible excretion of cholesterol as such is that of intestinal excretion. Such excretion occurs in the small intestine (34). However, despite the fact that an increased excretion of cholesterol is found in the feces of hyperthyroid animals (69) and in the hypercholesteremia produced by biliary obstruction (64), injection of cholate (33), or administration of Triton (61), there is no good evidence that plasma cholesterol can be either increased or decreased significantly by any change in its intestinal excretion.

D. *Destruction of Cholesterol*

Cholesterol was first shown to be destroyed in the animal body by Page and Menschick (135)—a finding subsequently confirmed by Schöenheimer and Breusch (153). Later, Bloch, Berg, and Rittenberg (23) demonstrated that one of the products resulting from the destruction of cholesterol in the dog was cholic acid. Byers and Biggs (30) confirmed their finding in the rat. Bergström and Norman (16) and Siperstein and Chaikoff (159) also observed the conversion of cholesterol to bile acid in the experimental animal.

The demonstration that cholesterol could be converted to cholate, while important, did not indicate necessarily that this is the body's manner of ridding itself of excess cholesterol. However, when a very great excess of cholesterol was given to rats in this laboratory, it was found (65) that this cholesterol was first stored in the liver, then *gradually* excreted as cholic acid. Thus it would seem from this last study that not only could cholesterol be converted to cholic acid but also that this reaction serves as a major mechanism by which the animal rids itself of excess cholesterol, a conclusion also arrived at independently by Siperstein and Chaikoff (159). In contrast to this, Magee (119) suggested that perhaps this conversion of cholesterol into cholate might not serve as a

major pathway for the riddance of excess cholesterol from the body. This conclusion was based upon his inability to detect an excess of cholate in the bile of dogs given cholesterol intravenously. Unfortunately, the amount of cholesterol given to these dogs probably depressed the rate of endogenous manufacture, as previously discussed, so that his animals were not confronted with an excess of cholesterol (as were the animals in our laboratory), hence no change in cholate excretion could have been expected. It is of interest, moreover, that after the employment of a different technique, the same author (120) now agrees with the conclusions concerning this matter originally propounded by this laboratory.

The major site of plasma cholesterol destruction is the liver and when this organ is removed, there is a marked inhibition in the animal's ability to rid its blood of administered cholesterol (65).

E. Summary of Normal Metabolism of Cholesterol

From the above data, a provisional schema can be established describing the various processes of cholesterol metabolism.

First, both the liver and the intestine (see fig. 1) serve as the chief suppliers of cholesterol to the blood. The former organ synthesizes cholesterol, a portion of which it discharges in a soluble form into the plasma and also in the bile. The small intestine on the other hand absorbs both biliary and dietary cholesterol, esterifies most of it in the presence of bile acid, and this absorbed cholesterol is incorporated in a chylomicron which reaches the blood exclusively via the thoracic lymph duct. This insoluble chylomicronous cholesterol then is either converted into soluble cholesterol by a clearing mechanism or ingested by the Kupffer cells of the liver and later transferred to the hepatic

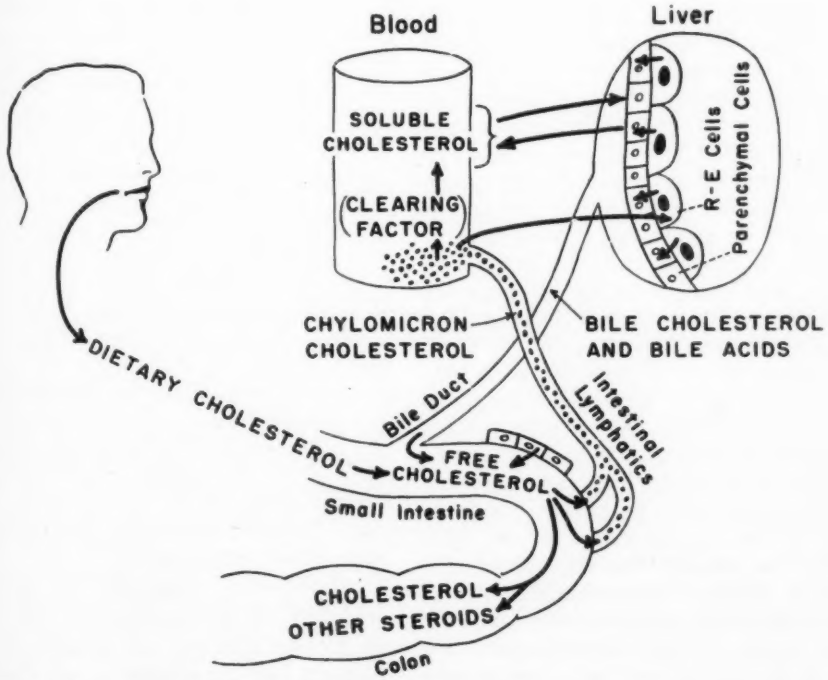

FIG. 1. Diagram illustrating metabolism of cholesterol.

parenchymal cells. The soluble portion of plasma cholesterol previously derived either from the liver or the solubilized chylomicron circulates in the blood to be later removed by the hepatic parenchymal cells, and then either stored, again discharged into plasma, or else converted and excreted in bile as bile acids. There seems, however, to be a continuous qualitative but not a quantitative interchange between the soluble cholesterol fractions of plasma, liver, and bile.

Regulation of plasma cholesterol level at any given instant theoretically should be a resultant of the rates of intestinal absorption, hepatic supply, and hepatic removal of cholesterol. Actually, however, as indicated above, there is little evidence that profound changes in plasma cholesterol level result except when there is interference with the third process—that of the hepatic removal of plasma cholesterol.

II. Pathogenesis of Hypercholesteremia

As mentioned above, a significant hypercholesteremia seems almost never to result from an increased rate of synthesis of cholesterol, an increased rate of absorption, or a decreased rate of intestinal excretion of cholesterol (38). The extreme hypercholesteremia produced in the rabbit by increased intake of dietary cholesterol at first glance might seem to negate this concept of ours, but even in this species the hypercholesteremia was found to be due not primarily to the increased absorption of cholesterol but to the relative inability of the rabbit to rid its plasma of *dietary* derived cholesterol (62).

Thus in the clinical hypercholesteremia associated with various liver disorders, hypothyroidism, pregnancy, and renal disorders, the fault seems to stem from the inability of the diseased person to rid his blood of cholesterol at the normal rate (38, 88, 148). Similarly in the experimental animal subjected to biliary obstruction, the animal given excess cholic acid *intravenously* and the animal given Triton intravenously, the hypercholesteremia resulting is due to some failure in the removal of cholesterol from plasma. In this connection, a group of workers recently found (58, 59) that following biliary obstruction or the injection of Triton an apparent increase in the rate of hepatic synthesis occurred. Their findings are not confirmed by those of Landon and Greenberg (107) who, on the contrary, found the rate of turnover of hepatic cholesterol *diminished* by bile duct ligation. These latter workers also found (107) the normal rate of synthesis of cholesterol in the rat to be much more rapid than previously reported; that is, they found a hepatic cholesterol half life of just under 24 hours (turnover time of 33.6 hours). Such a rate of synthesis is adequate to account for the excess cholesterol appearing in rat blood after Triton administration without the necessity of postulating any abnormal increase in rate. The hypercholesteremia actually results from a diminished rate of exit of cholesterol from blood (33, 61). After the intravenous administration of sodium cholate to the normal animal a similar "heaping up" of cholesterol in plasma occurs (33). Following the disappearance of either of these detergents from plasma, however, the barrier to the hepatic ingress of cholesterol is removed and the excess in plasma rapidly enters the liver.

From our studies of the animal subjected to biliary obstruction (31), given excess intravenous cholate (33), or Triton (61), it seems that the "heaping up" of cholesterol in blood is not due to any failure on the part of hepatic parenchymal cells to convert or otherwise destroy cholesterol. Therefore the plasma cholesterol of the hypercholesteremic animal must not be entering into the liver cell in a normal fashion. In a previous review (38) it was our belief that the plasma cholesterol of the hypercholesteremic animal was being abnormally retained because of an initial, intrinsic change in the plasma proteins usually carrying this steroid. We believed that this change was one of greater cholesterol adsorbability on the part of various plasma proteins. It is quite possible, however, that the change is one which may be viewed as a decreased protein adsorption

of cholesterol and that with such decreased adsorption, cholesterol molecules become less soluble, more particulate, less likely to leave the blood stream and enter the liver. Certainly, the latter concept would better explain the hypercholesteremic effects of various surface active substances (e.g., Triton and cholate) since these would tend to detach, not to attach, lipids and proteins.

The recent discovery of the clearing factor and its relationship to heparin or heparinoid substances (81) raises the question whether a derangement in this clearing mechanism may not be responsible for the "trapping" of cholesterol in plasma in hypercholesteremic states. It is of interest, particularly in connection with the above theory of possible decreased protein adsorption of lipid in hypercholesteremia, that the clearing of a lipemic serum proceeds simultaneously with an increase in those lipoproteins showing a high protein/lipid ratio (26). Regardless, however, of the possible importance of this system in post alimentary lipemia, the genesis of various hypercholesteremic states such as those associated with biliary obstruction (33), nephrosis (183), and Triton injection (61) are independent of the dietary intake of lipid.

Recently, as mentioned above, we have found that the Kupffer cell plays an important role in the removal from plasma and transference of dietary derived cholesterol to the hepatic parenchymal cell in all mammals studied to date. It seems, however, rather unlikely that a derangement of these cells could be the cause of all of the types of endogenous hypercholesteremia mentioned in the above paragraph for apparently, like the clearing factor mechanism, the Kupffer cells seem to be employed only in the disposition of cholesterol when in particle form (i.e., when in chylomicra).

Severe hypercholesteremia, with very few exceptions, then seems to arise from some change in 1) the physico-chemical status of the blood, 2) the efficiency of the hepatic R-E cells and/or the hepatic parenchymal cells, or 3) the cholesterol-protein aggregate itself which prevents the usual return of the steroid into the liver. It seems most likely at this time that the fundamental derangement is one involving the physico-chemical state of cholesterol—a derangement which now can be effected experimentally by the injection of surface active substances such as cholate (33), Triton (61, 94), and Tween (94), by excessive feeding of cholesterol to some species, and finally by the production of various disease states.

III. Possible Relationship Between Altered Cholesterol Metabolism and Atherosclerosis

Perhaps in no other disease entity is there a greater need than in atherosclerosis for openmindedness in the contemplation of its possible causes. Nevertheless, the impartial observer is constrained to conclude that such a state of mind is not always a common one in this field. Rather it would seem that some individuals or groups of individuals, deriving their impressions and drawing their conclusions from the *limited* data obtainable in their particular laboratories, endeavor to establish a single, dominant cause for the occurrence of atherosclerosis, even at the cost of overlooking or discounting other data which militate against the application or even the essential verity of their particular generalization. This, however, is not a necessarily tragic situation because if atherosclerosis is found ultimately to be a plant having divers roots, then perhaps many of these roots will have been well explored, indeed exploited. At this instant in time, however, it must be remembered that the tap root has still to be identified with certainty. With this reservation in mind, a brief survey of the problem of the possible interrelation of a deranged cholesterol metabolism to atherosclerosis can be made.

A. Available Evidence Suggesting the Relationship of Altered Cholesterol Metabolism to Atherosclerosis

There are five kinds of data which have been presented as evidence for the involve-

ment of cholesterol itself in the pathogenesis of atherosclerosis. These are 1) the presence of cholesterol in the atherosclerotic lesion; 2) the increased incidence of atherosclerosis in various clinical states of hypercholesteremia; 3) the findings of quantitative and possibly qualitative differences from normal of the plasma cholesterol transport in atherosclerotic individuals; 4) the experimental production of atherosclerosis by elevation of the plasma cholesterol; and 5) a seemingly close relationship between intake of dietary lipid (including cholesterol) and the incidence of atherosclerosis in various groups of people.

(1) *Presence of Cholesterol in the Atherosclerotic Lesion*

Although cholesterol was recognized as a constituent of an atherosclerotic plaque as early as 1847 (179), the first systematic study of the cholesterol content of atherosclerotic vessels seems to have been that of Windaus (189), who found that a series of atheromatous aortas contained 6 to 7 times as much free and over 20 times as much esterified cholesterol as normal aortas. One year later, Selig (157) analyzed similarly diseased aortas and found that their total lipid content was about 5 times that of normal aortas. This increased concentration of lipid and cholesterol in an atherosclerotic vessel has been confirmed repeatedly (110, 128, 155). Although there is a markedly increased concentration of both free and esterified cholesterol in such aortas, the ratio of each type of cholesterol therein is essentially identical with that found in the blood as Schönheimer first pointed out (128, 154). This, of course, suggests the blood origin of this cholesterol. As a matter of fact, Biggs and his associates (20) were able to detect in the atherosclerotic aorta of an individual a portion of the labelled cholesterol ingested by this same person, demonstrating the source of at least some of the cholesterol present in an atheromatous vessel. Nevertheless, the aorta is inherently capable of very rapid active biosynthesis of its own cholesterol (182).

(2) *Increased Incidence of Atherosclerosis in Various Clinical States of Hypercholesteremia*

There seems to be little doubt, despite Duff's arguments to the contrary (51), that clinical hypercholesteremia is associated with increased atherosclerosis. Thus in nephrosis (27, 90, 164), in hypothyroidism (29, 55, 150), and in familial hypercholesteremic xanthomatosis (1, 52, 173, 186) the disorders most often associated with hypercholesteremia, there is considerable evidence that there is an increased incidence of atherosclerosis. There is some disagreement, however, about the incidence of atherosclerosis in simple biliary obstruction with hypercholesteremia. Thus, MacMahon and Thannhauser (118) and also Bevans and Batchelor (17) believe that the disorder does promote the occurrence of atherosclerosis, whereas Duff (51) and Ahrens and Kunkel (2) were not able to detect a greater proclivity to atherosclerosis in their cases of this disorder. It is probable that some of this uncertainty stems from the relatively short duration of the disease process itself.

(3) *Possible Changes in Plasma Cholesterol Relationships in Atherosclerotic Individuals*

(*a*) *Possible Changes in Plasma Cholesterol Concentration*—Although, as mentioned above, there is virtual agreement that atherosclerosis occurs more frequently in the chronically hypercholesteremic individual, complete unanimity does not prevail concerning the possible converse of this relationship, namely that there is an increased incidence of hypercholesteremia in a group of atherosclerotic individuals free of other disorders specifically associated with hypercholesteremia.

On the whole, earlier workers (84, 106, 125, 136) were not able to detect sufficiently significant changes in the plasma cholesterol of atherosclerotic individuals to demonstrate that a close etiologic relationship existed between a hypercholesteremic state and atherosclerosis.

During the past decade however a number

of investigators (70, 82, 111, 129, 178) have presented statistical evidence purporting to indicate that the atherosclerotic state indeed is frequently associated with moderate hypercholesteremia. However, the association was one which had to be bolstered by statistical mathematics so slight at times were the differences between the blood cholesterol levels of the normal and the atherosclerotic groups. It is of course possible that the usually considered normocholesteremic level in individuals in Western Society may be actually a relative hypercholesteremia in contrast with that found in individuals of other groups or races (82).

(*b*) *Changes in Plasma Cholesterol/Phospholipid Ratio*—Because of relatively undramatic difference observed between the plasma total cholesterol of the normal and the atherosclerotic person, it was natural that a search was made for other relationships of cholesterol in the plasma of the atherosclerotic person.

Probably stimulated by the findings of Hueper (90), Boyd (25), and Ahrens and Kunkel (3) concerning the stabilizing role of phospholipids in plasma, Gertler, Garn, and Lerman (70) studied the cholesterol/phospholipid ratio in the plasma of atherosclerotic patients. They observed that there was an increase in the average cholesterol/phospholipid ratio of about 22 per cent in 60 patients with coronary artery disease. It is of interest however that the same group showed an average increase of 16 per cent in their total serum cholesterol. This finding of an elevated cholesterol/phospholipid ratio in atherosclerotic patients by Gertler and his associates has been confirmed by Barr, Russ, and Eden (12). Whether this observed increase in the cholesterol/phospholipid ratio in atherosclerosis however acts as a *primal and initiating* factor in the pathogenesis of atherosclerosis is completely unknown.

Perhaps the most suggestive evidence for the possible protective effect of a relatively high plasma phospholipid content is the observation that when such an elevation is achieved in the rabbit by parenteral administration of various detergents (e.g., Tween or Triton), considerable or even total protection is afforded the animal against the otherwise atherogenic properties of the hypercholesteremia (regardless of whether the latter is induced by ingestion of dietary cholesterol or by injection of the detergent itself). It is only fair to add, however, that the rabbit made hypercholesteremic by the injection of one of these detergents (Triton) differs from the rabbit made hypercholesteremic by ingestion of dietary cholesterol not only in having a higher plasma phospholipid level but also in exhibiting almost no microscopically discerned chylomicra despite the turbidity of the plasma (68). If the persistence of microscopically visible chylomicra bears some relationship to atherosclerosis (cf. Sec. (d) below), the protective action of Triton could be explained by this phenomenon.

(*c*) *Possible Abnormal Concentration of Specific Cholesterol Bearing Lipoprotein(s).*—Although it has been known for a long while that cholesterol is carried in plasma chiefly combined with the alpha and beta globulins (21, 156) and that the latter types of protein are increased in most hypercholesteremic states (113, 116, 117), the temporal relationship of such protein rises to most types of hypercholesteremia remains unknown. In cholesterol fed rabbits beta hyperglobinemia develops *pari passu* with the hypercholesteremia. Lewis and Page (112) called attention in 1947 to the fact that there were increased quantities of β globulin in normocholesteremic hypertensive subjects and animals.

However, Gofman and his associates (74, 75) announced in 1950 that they had observed a statistical correlation between a low density class of lipoproteins and the presence of atherosclerosis not only in the cholesterol-fed rabbit but also in the human subject. They believed too that this correlation in man was closer than that possibly existing between the total serum cholesterol or the degree of chylomicronemia. The authors also presented data which they believed suggested that in various human diseases known to be

associated with atherosclerosis (e.g., hypertension, diabetes, nephrotic syndrome, hypothyroidism, and xanthoma tuberosum) this same class of molecules was elevated. Later the same group of investigators suggested that the plasma concentration of this class of molecules chould be reduced by dietary means (92) and also by administration of heparin (80).

It seems fair to state that the publication of these articles has been of great value in stimulating new investigative interest in cholesterol and its possible relationship to atherosclerosis. Moreover, these same articles have provoked much work in areas of controversy which still remain to be resolved completely. These controversies have centered chiefly on the following questions:

1) Is the concentration of the lipoprotein moieties correlated with the incidence of coronary atherosclerosis?

2) If the above lipoprotein concentration is correlated with the incidence of coronary atherosclerosis, is it the best index of the presence of atherosclerosis?

3) Does the concentration of these particular species of lipoproteins have pathogenic as well as prognostic significance?

4) Can the concentration of these specific lipoproteins be altered by dietary and drug measures in such a fashion as to exert prophylactic and therapeutic benefit?

Concerning the first point, it seems probable but certainly not yet proved that in a *group* of male atherosclerotic patients, the plasma concentrations of Sf_{12-100} lipoprotein molecules will be significantly higher than in a group of supposedly normal individuals of the same age period. Thus the studies of Barr, Russ, and Eden (12), Gertler and Oppenheimer (71), Lewis and Page (114), and Keys (96) all tend to support in an indirect fashion this view of the Gofman group. On the other hand, Collens, Banowitch, and Colsky (42) were unable to detect in their 50 cases of proven diabetes and atherosclerosis any correlation between the serum concentration of the specific class of molecule and the presence of atherosclerosis.

Perhaps the greatest divergency in views centers about the second point. Although it is perhaps still too early to arrive at a final conclusion, it seems clear that the ultracentrifugal detection of the concentration of Sf_{12-100} lipoproteins does not represent either an infallible or even the best index of the presence of coronary atherosclerosis either in the individual or in the group. Thus Barr and associates (11, 12) point out that although an increase of the serum beta lipoproteins probably bears a closer relationship to atherosclerosis than a special subgroup (i.e., the Sf_{12-20} class), neither is free of the hazard of error in the diagnosis of atherosclerosis. Lewis and Page (114) agreed with this conclusion. Keys (95, 96) also concluded that the serum concentration of the specific class of lipoprotein molecules described by Gofman and his group bore no closer relationship to the incidence of atherosclerosis than did the total serum cholesterol. Labecki (105) in a study of 100 patients with myocardial infarction and 197 controls also found that the determination of either the serum total cholesterol or the chylomicron count furnished equally as good an index of correlation as the ultracentrifugal analysis of the lipoprotein classes present. Gertler and Oppenheimer (71) found a poor correlation of the specific class of lipoprotein molecules with the incidence of coronary atherosclerosis in women. Although additional data about this matter are now being obtained, examination of Gofman's own data suggests that the range of deviations is far too great to allow confidence in the clinical evaluation of the presence or absence of atherosclerosis in a given individual.

The third point of issue, namely the pathogenic or prognostic significance of a given concentration of Sf_{12-100} molecules in the serum is of course a matter which may take many years to determine. The strongest evidence in favor of the importance of this lipoprotein in the pathogenesis of atherosclerosis has been Gofman's finding of its increased concentration in those disorders known to be associated with increased athero-

sclerosis (e.g., hypertension and diabetes). Perhaps an additional bit of evidence is the decreased concentration of these lipoprotein classes in women at all ages prior to the menopause. However, Lewis and Page (114) found an elevation not in the beginning but in the later stages of hypertension apparently *after* vascular damage had occurred. Collens, Banowitch, and Colsky (42) moreover in their study of diabetic individuals *already suffering from arteriosclerosis* found results diametrically opposed to those of Gofman in that there was no greater concentration of Sf_{12-100} molecules in their patients than in the controls. Until such glaring divergencies can be reconciled, it seems unsafe to attach an unqualified pathogenic significance to the particular serum level of these lipoproteins in a given patient.

The fourth point at issue will require prolonged study before definite conclusions can be reached. On the other hand, there is little doubt that an altered diet or administration or heparin or estrogen can markedly alter the lipoprotein spectrum. It is of course obvious that the practical or therapeutic importance of this fourth point is based solely upon the verity of the first three.

(*d*) *Possible Abnormal Concentration or Persistence of Cholesterol in a Macromolecular State in Plasma*—Hueper in 1942 (91) reported a series of experiments in which he was able to produce atheroma-like lesions in the arteries of dogs by injection of such chemically dissimilar substances as pectin, acacia gum, and polyvinyl alcohol provided they were injected in the form of a macromolecular suspension. Seemingly, almost any substance could act in atherogenic fashion if it possessed and maintained a characteristic macromolecular size in plasma. Hueper later concluded (90) that perhaps cholesterol too might form similar atherogenic aggregates and then precipitate out as a film upon the intima of arteries thus initiating the atherosclerotic process. This concept was essentially agreed to by Hirsch and Weinhouse (89) who believed that an increase in the particle size of the plasma lipoprotein aggregates probably was the first step in the pathogenesis of atherosclerosis. None of these investigators could have been aware of the recently discovered fact (35) that almost all *dietary* derived cholesterol also circulates as a large aggregate in plasma until it is either disintegrated by the clearing factor mechanism (5, 8, 83) or ingested by the hepatic R-E cell (54, 67).

Moreton (127) however, sensing that chylomicra did contain cholesterol, strongly insisted that abnormal persistence of this aggregate in blood was the essential cause of atherosclerosis in man. It is of interest that Becker, Meyer, and Necheles, as well as Zinn and Griffith, have presented evidence which strongly suggests that there is an abnormally slow disappearance of such chylomicra both with advancing age (14) and in atherosclerosis (194). Block, Barker, and Mann (24) also give indirect and partial support to Moreton's concept for they have observed a reduction in the clearing mechanism of atherosclerotic individuals; such clearing of course is equivalent to the dissolution of large macromolecular aggregates or chylomicra.

Despite the above confirmations, there has been no widespread acceptance of the possible role of prolonged chylomicronemia in the pathogenesis of atherosclerosis. In part this has been due to the relatively indirect nature of the positive data referred to above. Also Gofman and associates (74) seemingly could find no correlation between the concentration of chylomicrons and the atherosclerosis of his patients. However, it is doubtful (the authors give no details of their study) whether they actually performed a *series* of plasma analyses *after* the ingestion of a given amount of cholesterol, a procedure quite necessary before judgment could fairly be made.

Swank and Wilmot (168) reported that only a small fraction of the total plasma cholesterol was found in the chylomicra even after ingestion of cholesterol. Their data are probably correct but the authors neglected to mention that their analysis of the chylomicra

in plasma at a given instant represents only a small fraction of the total amount of cholesterol continuously carried by chylomicra over a period of many hours from the gut to the liver. Thus their data could not show what was later discovered when the chylomicra of lymph also was analyzed, namely, that almost all dietary derived cholesterol enters into the blood enmeshed in chylomicra.

This latter finding, of course, carries a different significance than that allowed by the almost negative results of Swank and Wilmot, for regardless of the concentration of this chylomicron cholesterol in plasma at any point in time, it serves as the initial mode of transport of all cholesterol derived from the diet. Moreover, as was pointed out above, this cholesterol not only differs in its physicochemical characteristics from endogenously produced cholesterol but must be handled in part at least differently by the body (i.e., by the hepatic R-E cells).

In view of the above newly discovered data, plus the fact that even experimentally induced atherosclerosis depends upon the absorption of dietary cholesterol, perhaps it would be wise not to dismiss the findings of Moreton, Becker, Meyer and Necheles, Zinn and Griffith, Block, Barker and Mann, or the conceptual conclusions of Hueper and Hirsch and Weinhouse. The possible etiologic relationship of hyperchylomicronemia to atherosclerosis, while not proved, still offers the investigator possibilities of productive research.

(4) *Experimental Production of Atherosclerosis by Elevation of the Plasma Cholesterol*

Perhaps no single experimental study did as much to incriminate cholesterol in the pathogenesis of atherosclerosis as the monumental one of Anitschkow (7), in which he demonstrated convincingly that the rabbit became rapidly atherosclerotic after a few weeks of cholesterol feeding.

Despite this clear-cut experimental demonstration of the pathogenic capabilities of dietary cholesterol, there was no precipitous change in the thought of most investigators concerning the etiology of human atherosclerosis. The general unsuitability of the rabbit for physiologic study, the fact that cholesterol was not a normal food constituent for this animal, the seeming necessity for the induction of profound hypercholesteremia before atherosclerosis would occur, the generalized infiltration of cholesterol into all organs concomitant with the atherosclerosis, and failure at first to induce similar atherosclerotic lesions in other mammals; all of these facts indeed seemed to indicate that the finding of Anitschkow had an importance chiefly of interest to the general biologist rather than to the pathologist concerned with human atherosclerosis.

Later, however, with the induction of atherosclerosis in the guinea pig (10), the dog (165), and the fowl (45, 177), the uniqueness of the rabbit aortic lesion began to be considered as due not to the species but to the chemical substance, cholesterol itself. Then when the other data to be described below were collated, a new retrospect importance was given to Anitschkow's pioneer achievement. Certainly there is no doubt now that if the plasma cholesterol of most animals is elevated high enough and long enough and if some or most of this cholesterol is derived from an exogenous source, atherosclerosis will result. Only the rat remains the exception and this may be because it and not the rabbit reacts uniquely (62) to an elevation of its plasma cholesterol. It is only fair, however, to state that up to now it has not been reported possible to maintain a rat in a greatly elevated hypercholesteremic state over many months, although a moderate hypercholesteremic state has been attained in this animal (133, 146) without atherosclerosis resulting.

Although the other mammals cited above are susceptible to atherosclerosis after cholesterol feeding it is a susceptibility which has spatial limitations within the vascular system in that the cholesterol laden placques are concentrated in the systemic portion of the circulation and in those areas of the latter where turbulence and stress may be the

greatest (aorta, the coronary arteries, and about the orifices of intercostal arteries). Thus, in the low pressure pulmonary circulation of these cholesterol fed animals, little or no atherosclerosis results. Furthermore, administration of estrogen has been reported recently (138) to spare the coronary vasculature of the cholesterol-fed fowl, although it does not decrease the extent of aortic atherosclerosis. It would seem then that although a cholesterol laden plasma is the *sine qua non* of dietary induced atherosclerosis, the site and to some extent the degree of the latter are determined by various other factors.

(5) *Possible Relationship Between Ingestion of Dietary Lipid (Including Cholesterol) and Incidence of Atherosclerosis*

If dietary cholesterol or lipid bears an important relationship to the occurrence of atherosclerosis in man, then it is almost self evident that no single phase of the total problem could offer such definitive information as carefully controlled, unbiased studies of the incidence of atherosclerosis in various groups of individuals who differ from each other only in respect to their dietary intake.

Such a study to be truly valuable to this field of investigation would have to take into account and rigidly control not only the quantitative and qualitative aspects of the diet but also other facts which today are known or suspected as favoring the occurrence of the atherosclerotic process. These are: 1) incidence of hypertension endogenously induced, 2) incidence of hypercholesteremic disorders, 3) hereditary and familial tendencies, 4) tobacco habits, and 5) incidence of environmental emotional stress and strain.

Besides these 5 factors, it is perhaps necessary to consider the economic, cultural, and social features of various groups whose food habits are being studied. Certainly there are differences other than dietary which also characterize and distinguish a South African Bantu from a New York corporation executive. Is it fair then to attribute his relative immunity to atherosclerosis only to his dietary peculiarity? Perhaps our emphasis here upon the employment of a total perspective in the amassment of statistics concerning the relationship of dietary habits and atherosclerosis may seem irrelevant at first glance but in the literature cited below, the need of such breadth of study becomes manifest.

Thus, Anitschkow (6) and later Wilens (184) report the low incidence of atheromatous disease in the Costa Rican inferring that his low lipid dietary was responsible. However, the Central American Indian differs also from his North American neighbors in his gentle, unflurried, rather tranquil personality. Moreover, there is a relative absence of hypertension in this type of individual (122), and his immunity to atherosclerosis could just as well be ascribed to this latter phenomenon as the absence of lipid in his diet.

Again Oppenheim (132), Rosenthal (151), and Snapper (162) have reported upon the low incidence of atherosclerosis in the Chinese (particularly those living in Southern China), and the latter two authors again point to their low lipid intake and stress its possible causal relationship to their relative immunity. Before, however, the dietary factor alone can be given this importance, data concerning the other factors mentioned above also would have to be obtained and evaluated. For example, the relative rarity of hypertension in this same group (40, 56, 57, 102, 115) alone makes it an unsuitable one for comparison with groups having a high incidence of hypertension (i.e., Americans and Europeans).

Similarly, the rarity of atherosclerosis in the Okinawan has been linked inferentially with his low lipid intake both by Steiner (166) and Benjamin (15). Perhaps it would be justifiable to use this difference as the only important deviant in his living as compared to an American and overlook his small tobacco consumption and his placid, tranquil temperament. However, the rare incidence of hypertension in the Okinawan cannot be similarly overlooked and because of this it is

not possible to ascribe to his diet alone his relative immunity to atherosclerosis as compared to the American whose incidence of hypertension is high.

Much also has been made of the fact that the nomadic Kirghiz tribesman ingests a lipid rich diet and suffers extensively from atherosclerosis (104). Authors using this tribe's predisposition to atherosclerosis as an argument for the importance of dietary lipid in the pathogenesis of atherosclerosis might be permitted conceivably to discount any possible connection between the turbulence and insecurity of the Kirghiz personality (13) and their atherosclerosis. But certainly the high incidence of hypertension in this same tribe (as indicated by the frequency of occurrence of apoplexy and contracted kidneys (104), does not give them the authority to blame all cases of atherosclerosis upon the diet alone—unless these same authors demonstrate that the high incidence of hypertension too stemmed from lipid overindulgence.

A similar criticism of an overemphasis upon a single factor also might be levelled against those who refer to the decreased mortality statistics of various populations whose lipid dietary temporarily has been restricted. Although the observations of Aschoff (9) concerning the decreased incidence of atherosclerosis in Germans during World War I and those of Malmros (121), Dedichen and associates (46), and Ström and Jenson (167) concerning Norway, Finland, and Leningrad during World War II may be correct, it must be remembered that before a lowered intake of lipid can be adjudged as the cause, it must be demonstrated that it was the only other concomitant variant. However, there was also a reduction in cigarette smoking in the occupied countries (167), a probable change in stress patterns (e.g., possible transference of individual anxieties to those of a group), and a marked decrease also in deaths due to nephritis, hypertension, and all forms of endocarditis (167). The possibility exists too of a marked decline in the diagnostic precision of war-harassed physicians.

Indeed some of these factors have been considered by several investigators. Thus Pihl (139) stresses the fact that the fall in mortality rates began in Norway before the dietary restriction. Dedichen and associates (46), puzzled about the abrupt decline in wartime Norway of fatalities not only due to atherosclerosis but also to metabolic and even infectious disorders, have suggested that the decreased incidence of thromboembolic accidents also observed during the same period might have been responsible for the lessened mortality rate of cardiovascular and other types of disease.

Besides the above difficulties attending any efforts to ascribe to decreased lipid ingestion alone the responsibility for the fall in deaths due to atherosclerosis in the war torn countries, there is the fact that there were serious discrepancies in the waxing and waning of the dietary on one hand and the mortality rates on the other. Thus, examination of Malmros' data (121) indicates that although the dietary intake of fat in Finland continued to decrease continuously from 1940 to 1947, the death rate from atherosclerosis decreased only from 1940 to 1943 and then began to rise again. Moreover, in Sweden from 1935 to 1940 the lipid intake did not increase, and in the United States from 1940 to 1947, the lipid intake actually decreased (121), but nevertheless the mortality rates in both countries continued to rise.

More recently Keys and his associates (95, 97, 98, 99) have studied the dietary and the blood cholesterol level of the inhabitants of various countries including the United States, England, Canada, Australia, Italy, Spain, and Portugal. From his studies, Keys believes the evidence is clearcut that the general intake of fat is higher in the United States than that in any other country; the blood cholesterol of an individual over 30 years of age rises in proportion to the dietary intake not of cholesterol but of fat; and a parallelism can be shown between the fraction of a country's dietary and its mortality rate from

degenerative heart disease (coronary disease, angina pectoris, infarction, chronic myocarditis, and myocardial degeneration). He believes that when this evidence is conjoined with two clinical observations, viz, that hypercholesteremic disorders predispose to atherosclerosis and that patients with coronary artery disease usually exhibit an elevated blood cholesterol, the conclusion may be justified that a high fat dietary may be atherogenic.

It is our belief that the observations of Keys and his colleagues are certainly sound but the inferences derived therefrom may not be completely justified. As Keys has stated, those countries exhibiting a high incidence of coronary disease also exhibit a high incidence of all types of circulatory disease including hypertension. This increased incidence of hypertension alone, as stressed above, would lead to an increase in the incidence of and deaths due to atherosclerosis. Furthermore, the population of the United States differs from that of Italy for example in many other respects than just the ingestion of a high fat diet. The American population smokes more; it has, as Keys infers, a much larger middle class; it has a far higher incidence of hypertension, and a much more accelerated pace of living. It is unfortunate too that Keys was forced to compare the electrocardiographic features of a group of lower class Italians with those of a group of successful Minnesota business men and corporation executives.

The possible error inherent in attention to only one characteristic of a race or group may be illustrated by the fact that if certain other characteristics are used, it is also possible to find a parallelism between their incidence and the absence of atherosclerosis. For example, if one studies the incidence of atherosclerosis in races or groups who are relatively immune to nervous stress and strain (either because of environmental or constitutional factors) and hypertension, there is a similar immunity to atherosclerosis.

Thus certain tribes of African negroes exhibiting a minimum of emotional stress and relatively immune to hypertension were found to be almost free of atherosclerosis (49, 50, 187, 188). Yet these negroes ate generously of lipid containing foods (49, 50).

Eskimos too are singularly immune to emotional tension (53) and to hypertension (4, 174). They likewise seem rarely to exhibit either clinical (174) or electrocardiographic evidence (4) of coronary atherosclerosis. Furthermore, despite their high intake of lipid (53, 85, 174), they have a blood cholesterol either as low or lower than the average North American white person (4, 44, 158).

Finally, the Navajo Indian, relatively free of emotional stress and strain and almost completely free of hypertension, if he is under the age of 40 (41), has been found recently by Gilbert (73) to be almost free of coronary artery disease. The diet of the Navajo, however, is not low in either cholesterol or lipid (73). The high incidence of gall bladder disease in this tribe (73) moreover suggests that they are not intrinsically immune to disorders related to cholesterol derangements.

We have not stressed the reported rarity of atherosclerosis in these three groups of unhurried, less tense, normotensive persons subsisting upon a high or moderately high lipid-cholesterol diet to disprove the latter's possible atherogenic propensities but to point out that there is not always a parallelism between the intake of lipid and/or cholesterol and the incidence of coronary atherosclerosis; other factors may exhibit an even closer relationship, and it is dangerous to narrow one's study of possible causes of a disorder to only a survey of the eating habits of a race or group. Indeed it seems that many American laymen, according to our personal observations, believe that the peculiar type of stress and tension to which they are exposed plays a more important role in their possible earlier demise (97, 98) than their fat or cholesterol intake. Perhaps this unscientific foreboding on their part is completely unfounded but certainly it cannot be dismissed until the trained investigator at least admits the presence of emotional tension in certain groups (particularly the executive group) and

attempts to study its possible atherogenic importance. Admittedly this is a formidable task primarily because of our present inability not only to duplicate a comparable type of stress in the laboratory animal but even to express its intensity in acceptable quantitative terms when observed in the human individual. It is also particularly difficult for the present day laboratory researcher to envision the possible mechanism whereby an emotion might alter the structure and substance of an artery.

Until all of these difficulties are overcome however, a receptive openmindedness distinctly is to be desired. Certainly, the present reviewers are forced to conclude as did Weiss and Minot (180) and later Duff (51) that the possible relationship between lipid and/or cholesterol intake and the pathogenesis of atherosclerosis is beclouded by the presence of other complicating factors. Indeed were it not for the other experimental observations (cited in previous sections) relating cholesterol to atherosclerosis, the inferences derived from the dietary data so far amassed would have to be discounted almost completely. However, in view of these other observations, the apparent parallelism of a high lipid and/or cholesterol intake and atherosclerosis in some groups (despite the probable presence of emotional surcharge and hypertension also in these same groups) must be considered as more than coincidental. Even with this assumption however, the fraction of responsibility of the lipid in the total picture of atherogenesis may be only one of intensification of an already rapidly developing process.

IV. Possible Relationship of Intrinsic Arterial Derangement To Atherosclerosis

The physiologist and biochemist should not overlook or put aside data obtained by the pathologist which taken in their entirety, strongly suggest that cholesterol may play only an accessory role in atherosclerosis and perhaps an even lesser one in the arteriosclerotic process. It is not prudent, for example, for the worker in this field to overlook the well-established fact that whenever a blood vessel is traumatized, whether such trauma is due to an increase in blood pressure, intravascular turbulence, inflammation, or vasospasm of the vessel, atherosclerosis is a frequent sequel and this may occur regardless of the age, the type or state of nutrition or the plasma cholesterol concentration of the subject.

Thus, systemic atherosclerosis as already observed above is many times more frequent and more severe in the hypertensive individual. In the patient also with increased pulmonary hypertension, atherosclerotic infiltration of the pulmonary artery frequently occurs (48, 109). Similarly, the turbulence set up in an artery emptying into an arteriovenous aneurysm usually induces a localized atherosclerosis (47). Frequently, vasospastic drugs induce atherosclerosis in the vessel at and only at the site where this vessel was damaged by these same drugs (51). Furthermore, xanthelasma is a phenomenon which when it appears in a normo-cholesteremic individual is commonly preceded by a change in the skin about the eye as indicated by a dense melanin deposition. Furthermore, cutaneous xanthoma occurring in primary xanthomatosis commonly appears in skin area of trauma. In other words, *there can be no gainsaying the fact that cholesterol is one of the body's most ubiquitous infiltrants of previously deranged tissue.* On the other hand the evidence is not so clear-cut that cholesterol itself *initiates* tissue damage, although the intimal changes in the aorta of the cholesterol fed rabbit certainly suggest this possibility as Duff emphasized (51).

The above observations suggest caution in attributing to cholesterol the supreme role of initiating atherosclerosis. In addition, the descriptions of the coronary vasculature of patients dying of coronary artery disease published by Yater and associates (193), French and Dock (60), Moschcowitz (130), and Moon and Rinehart (126) all bear one similarity, namely that a diseased but not yet occluded branch of a coronary artery ex-

hibits not a visible cholesterol deposit or infiltration but a fibroblastic proliferation of intima. Later, detectable cholesterol appears in the depths of such lesions. If this intimal proliferation actually preceeds the typical atherosclerotic lesion, then cholesterol itself must be considered as playing a secondary, infiltrating role—unless it can be shown that an altered plasma cholesterol itself can *initiate* such hyperplastic, dysplastic changes in the intima. The failure, however, to find cholesterol by Sudan staining of such hyperplastic intimas does not indicate necessarily that cholesterol is absent—it means only that the cholesterol possibly present is not in the proper physico-chemical state to be stained—similar, for example, to that moiety of cholesterol present but not stainable in the liver of the starved rat (67). Certainly it is obvious that the answer to this particular point is of tremendous importance in any assessment of the total role of cholesterol in the production of human atherosclerosis.

V. Discussion and Summary

A collation of all the foregoing data allows the formulation of certain concepts concerning not only normal and deranged cholesterol metabolism but also the possible relationship of the latter to atherosclerosis.

First, it seems clear that the liver is the one organ whose role is overwhelmingly primal in the disposition of plasma cholesterol, since it is this organ which synthesizes and discharges free cholesterol into the bile and blood, later absorbs a portion of the free cholesterol to store it, esterify it, or convert it into cholic acid and excrete it. This same organ also takes out the cholesterol coming to it from the gut either after it has been solubilized by the clearing factor mechanism or still remains enmeshed in its chylomicron envelope. However, apparently only the Kupffer cell of the liver can effect removal of cholesterol when it is in this latter physico-chemical state.

Second, when a derangement in the control of plasma cholesterol concentration occurs and the cholesterol rises in the plasma, it seems to be due to some form of trapping or heaping up of cholesterol in blood. It is rarely, if ever, due to an increase either in rate of synthesis or absorption of cholesterol nor conversely due to a decrease in the biliary or intestinal excretion of this substance. The causes of this excess accumulation of cholesterol in plasma remain to be discovered but perhaps an alteration in the physico-chemical status of plasma cholesterol or in the protein fractions carrying it may be the most important mechanism. More recently our own observations suggest the possibility that the hepatic reticulo-endothelial system may be involved in some forms of hypercholesteremia.

Third, it seems reasonably certain that when a severe degree of hypercholesteremia occurs in man, an increased incidence of atherosclerosis may be expected. It is only fair to add that this relationship is not always a dramatically striking one and is even denied by some competent observers.

Fourth, although there is no uniformity in agreement about this point, most modern observers are inclined to believe that when *considered as a group*, atherosclerotic individuals exhibit a slight elevation of plasma cholesterol. Considered as a group again, such individuals also tend to exhibit an increased cholesterol/phospholipid ratio, an increased content of Sf_{12-100} lipoprotein molecules and a higher chylomicron index. It is our opinion that the statistical validity of such increases hold good at best only for the group. Whether, however, any of these determinations have any diagnostic or prognostic value as to the present or expected occurrence of atherosclerosis in a given person is a matter which has yet to be proved.

Fifth, atherosclerosis can be experimentally produced only in certain animals and under certain conditions of which the inducement of hypercholesteremia is an indispensable requirement. However, the hypercholesteremia seemingly must be primarily produced or accompanied by the ingestion of dietary cholesterol. Thus the blood level

of cholesterol in the rabbit may be elevated by injections of Triton or Tween to extreme levels but little or no atherosclerosis will result if the animal is not allowed to ingest cholesterol. Our own findings of the different physico-chemical status of dietary derived cholesterol as it enters the blood as compared to that of liver produced cholesterol make us believe that the intermittent but chronic exposure of arterial intima to cholesterol in chylomicron form may be the chief cause of the atherosclerosis found in the cholesterol fed rabbit, and it may have considerable bearing in the genesis of those cases of human atherosclerosis which seemingly stem from an antecedent chronic hypercholesteremia.

Sixth, no definitive support is afforded by presently available data for the hypothesis that the increased intake of dietary cholesterol and/or fat leads to an increased incidence of atherosclerosis. Indeed the data when critically reviewed offer a dramatic confirmation of a phenomenon already known, namely that when hypertension is present, atherosclerosis flourishes, and when it is absent, the latter dwindles, even in the face of a high lipid intake.

Finally, it seems clear enough that whereas the presence of cholesterol in blood can and does convert intimal lesions at first purely proliferative or degenerative into those typical of atherosclerosis, there is almost total ignorance concerning the relative importance of each of these factors (the intimal lesion and the cholesterol infiltration) in the pathogenesis of the full fledged lesion. There are pathologists who believe that quantitative or qualitative changes in transport of cholesterol are of trivial importance compared to the histologic changes occurring in the vessel wall which then favor the deposition of cholesterol. This impasse between that which pathologists believe they *see* in the arteries of man and that which physiologists believe they *produce* in the arteries of animals by cholesterol feeding can only be resolved by a willingness of both groups to accept the possible occurrence of *multiple factors at play* in the pathogenesis of atherosclerosis. A fine first step in such a resolution would be the efforts of physiologists to produce experimentally in the absence of hypercholesteremia by various possible means what the pathologists see, namely, the initially diseased but seemingly cholesterol free artery. Until this is done, the pathogenesis of atherosclerosis can only be described as illustrated below:

$$\text{Time} \times \left(\begin{array}{c}\text{Intrinsic (?)}\\ \text{Intimal}\\ \text{Derangement}^*\end{array}\right) \times \left(\begin{array}{c}\text{Quantitative and}\\ \text{Qualitative Alteration}\\ \text{of Plasma Lipids}\\ \text{Including Cholesterol}\end{array}\right) \times \left(\begin{array}{c}\text{Blood}\\ \text{Pressure}\end{array}\right) = \boxed{\begin{array}{c}\text{Atherosclerosis}\end{array}}$$

*Primary or secondary to cholesterol infiltration

This diagram suggests that an increase in the magnitude in one of the factors alone may produce or increase the extent of atherosclerosis without the necessity of any particular deviation from normal of the other potential factors. Thus, for example, if the blood pressure is below 40 mm. Hg. (as usually occurs in the pulmonary system), there will be little atherosclerosis despite possible plasma cholesterol changes and the duration of such changes. On the other hand, if the blood pressure is abnormally high as in hypertensive individuals, atherosclerosis occurs even with a complete normality of all plasma lipids.

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BOOK REVIEWS

PARENTAL AGE AND CHARACTERISTICS OF THE OFFSPRING, vol. 57, art. 5, Annals of the New York Academy of Sciences, 1954, consulting editor, Leonell C. Strong; 22 papers, 150 pages, paper bound, $3.50.

It is always with pleasure one takes notice of a new issue of the Annals of the New York Academy of Sciences. The monograph series covers a wide variety of rather special topics. Common to most of its volumes is the wide scope of the studies presented and the great actuality of the subject matter. This holds true also for the monograph resulting from papers read at an international conference proposed by Strong on "Parental Age and Characteristics of the Offspring." The concept of parental age as heading for this monograph has been used in the widest possible sense: any processes connected with the production of a new independent organism and containing a time factor may be considered as some sort of parental aging. Thus in botany parental age may mean the age of the meristem which gives rise to daughter fronds but also the seasonal "age" of the plant which produces seeds, or the time of storage of the seeds before germination. Likewise in animal experimentation parental age is used both in its conventional sense and in a wider one. Thus the effects of "aging," i.e., "overripeness" of the gametes before fertilization, are dealt with. From this liberal use of the term, a field which still may be considered as nearly unexplored has gained in richness and interest obviously more than would have been possible if a more strict adherence to the concept of parental age were adopted.

The first paper contains a summary of the well known studies of Lansing concerning a nongenic factor in the longevity of Rotifers. The elegant method of study reveals a cumulative but reversible aging factor which reduces the life span in successive orthoclones derived from old mother rotifers. The reader is thereby made to anticipate only deleterious effects of high maternal age, but already in the next paper this anticipation is shown to be partly erroneous. Hauschka and Brown present evidence of a decreasing frequency of an eye defect, "eyelids open," in new born mice with advancing litter seriation. The same favorable influence of maternal aging is demonstrated by Searle to hold true for certain skeletal malformations occurring in mice and by Law for experimental leukemia in mice. The mechanisms responsible for these different manifestations of parental influence, whether genic on nongenic, are still obscure. Only in the leukemia of mice a maternal resistance factor is known to be contributed both before birth and through mothers' milk. Strong's studies dealing with the appearance of chemically induced fibrosarcomas in three sublines of mice (original, early litter descents, and advanced litter descents) open a new approach also to the problem of cancer incidence in human populations. The shorter latency in females of the early litter series: 98 ± 1.56 against 126.0 ± 2.13 in the advanced litter series is highly significant.

Most of the other papers open a less favorable view on the process of parental aging. The effects on development when eggs and sperm are aged before fertilization are dealt with in a paper by R. J. Blandau. Overripeness of the eggs leads to increased incidence of malformations in amphibians, in fishes, and in some evertebrates, e.g., the sea urchin. In several mammals there is a gradual reduction in the fertilizable life of the ovum as the period between ovulation and insemination is prolonged. After implantation the overripe egg may be retarded in its development or may die before the fetal period is reached. Whether moderate overripeness of the mammalian egg leads to definite teratogenic development in the fetal and postnatal period is as yet unexplored.

The paper of D. P. Murphy dealing with the birth of malformed children in relation to maternal age clearly demonstrates the constancy of the ratio of malformed children to normal children in the offspring of mothers under 30 years of age and its rapid increase beyond that age.

The problem of mongolism ("the outstanding condition in the human being in which advanced maternal age can be shown to be associated with an abnormal characteristic in the offspring") is dealt with in two papers, the one by Penrose, the other by Ingall. Although the causative mechanisms operating with the production of mongoloids is not fully understood, maternal constitutional abnormalities like retroflexion of the uterus or other unfavorable intrauterine conditions during pregnancy may be considered as possible factors. These papers therefore lead one to ask whether altered physiologic states during pregnancy may affect the offspring. Wilson offers a most interesting experimental approach to this question. By studying in rats the effects on the embryos of various types of stress in the mother during pregnancy, he was able to show that not all forms of physiologic alterations, however severe, may be capable of affecting the characteristics of the offspring which goes to term. Thus deficiency of vitamin A, while not causing any maternal deaths, affected the embryos; 78 per cent of those who reached term were malformed whereas severe haemorrhagic anaemia and carbon tetra-

chloride poisoning, both causing high maternal mortality, had very little or no effect on the young in litters that reached term.

A paper by Treffers deals with the rather intricate problem of the influence of maternal age on immunity of the offspring. This problem involves three biologic interacting factors: 1) The ability of the mother to produce anatomically complete and physiologically normal offspring; 2) The ability of the mother to manufacture and transmit to the offspring the specific antibodies necessary for resistance during early infancy; 3) The ability of the mother to transmit to the offspring infectious organisms, antigens, or other agents which may induce in these offsprings either a pathologic condition or a specific immunity. The need for further data and analysis is stressed.

Maternal behavior in animals is considered by Riess and by Sawin. The racial differences in maternal behavior demonstrated by Sawin are most striking and obviously complicate the problem. The viability of the offspring is likewise differently affected by maternal age in different races. Russell illustrates the use of IBM cards for routine recording of characteristics of the parents of a given individual in a mouse colony.

Aging in plants is dealt with in three papers. Ashby and Wangermann present interesting evidence of aging in the meristem of *Lemna minor*, which leads to a progressive diminution of size in successive daughter fronds. These again produce large daughter fronds at the beginning of their independent life. It is supposed that the meristem possibly manufactures a humoral agent which promotes growth in the daughter frond. The amount of this agent, however, decreases with age. Biophysical seasonal factors affecting the activity of seeds is demonstrated by studies of Bünning. Blakeslee presents a highly interesting comment on the mutation rate in stored seeds. In laboratory stored seeds the mutation rate shows a marked increase with aging but in seeds buried in dry soil no such effect is manifested. The moisture and high temperature seem to be predisposing factors for the occurrence of mutations. One is therefore tempted to ask: if there is no metabolism is there no aging?

A paper by Takahashi demonstrates the influence of parental age on the sex ratio at birth in Japan. An almost regular decline of the sex ratio occurs with advancing parental age up to the age of 40 to 45; beyond that age the sex ratio increases enormously. Whether this is a social or a biologic effect the author refrains from concluding.

The collection of these papers forms a most stimulating and interesting entity, although the reader wonders why the papers are not arranged in some orderly sequence according to the subject matter. As it is, the sequence is quite random except that an excellent summary by Cowdry concludes the book.

The monograph should be read by every gerontologist—it aids in demolishing some rigid habits of thought and suggests new experimental and statistical approaches to the general problems of aging.

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SYMPOSIUM ON PROBLEMS OF GERONTOLOGY, Robert S. Goodhart, Editor, The National Vitamin Foundation, New York, 1954, 141 pages, $2.50, paper bound.

It is probably correct to say that the best efforts toward advancing the science of gerontology have been those devoted to the wide dissemination of whatever facts are learned about the subject. The distinct scarcity of competent laboratory scientists willing to work in this discipline has resulted in relatively few outstanding contributions. For the present, gerontologic biology seems to be a discipline with "more chiefs than Indians" and the recognition of this fact by the older workers in the field leads to constant efforts to propagandize the other biologic sciences in calling for more cooperation and collaboration from experts in other fields.

The Symposium on Problems in Gerontology was arranged by Dr. Bacon F. Chow and Dr. N. W. Shock and seems to be another successful promotional effort to interest competent scientists from various medical disciplines to examine their data for possible leads which could be helpful in understanding the process of aging. Those able veterans in gerontology, J. E. Kirk, A. I. Lansing, H. A. Rafsky, and N. W. Shock reported on vitamin levels, senescence as a sequel to adolescence, nutritional problems, and biochemical aspects of aging, respectively. The booklet also contains reports by H. J. Deuel, Jr., on fat metabolism, C. S. Davidson on protein metabolism, B. F. Chow on B_{12}, F. H. Bethell on hemopoietic factors, C. N. H. Long on hormones and metabolism, and D. J. Ingle on endocrine stress. Some refreshingly new perspectives are presented by the latter group and so we might say that the mission of the "elders" was successfully accomplished.

This booklet reinforces a definite impression that gerontology is successfully bridging the gap between the philosophic and the experimental approach. There are fewer implications of successful clinical treatments and more discussion of attempts to make basic measurements.

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BOOKS RECEIVED

Books received since September 1, 1954, are acknowledged in the following list.

Geriatric Medicine, Medical Care of Later Maturity, 3rd edition, edited by Edward J. Stieglitz, J. B. Lippincott Company, Philadelphia, 1954, 718 pages, $15.00.

Myocardial Infarction, by Irving S. Wright, Charles D. Marple, and Dorothy Fahs Beck, Grune & Stratton, Inc., New York, 1954, 656 pages, $8.50.

Proceedings of the Annual Meeting, Council for High Blood Pressure Research of the American Heart Association, 1953, International Press, New York, 1954, 94 pages, $2.00 from the American Heart Association, Inc., 44 East 23rd St., New York.

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Section B

Psychological and Social Sciences, Social Work and Administration

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THE MAINTENANCE OF INTELLECTUAL ABILITY IN GIFTED ADULTS

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ALTHOUGH numerous studies have shown a tendency for adults to exhibit decreasing intellectual abilities (as measured in test scores) with age, the amount of the decrement has been found to vary with the nature of the measuring instrument. In fact, several investigators have found slight but consistent increases up to about 60 years of age in scores earned on tests of vocabulary or word knowledge. These increases have been found to occur in populations of above average ability and education, and in tests that do not put a premium on speed of performance. The increases do not seem to hold for tests that require fast reactions, or for persons of low intelligence.

In a recent summary of research on changes in intellectual function with advancing age, Shock (5) has pointed out that several researches give evidence of significant changes in mental organization with age; that very few studies have been made in which the same subjects have been retested after a lapse of time; and that most of the tests used are inadequate to differentiate changing abilities at the upper levels of intelligence. Several studies published since Shock's summary give important information bearing on the relation between age and score in adults. Owens (4) retested 127 college men on the Army Alpha after a lapse of 31 years. Corsini and Fassett (2), in a study of Wechsler-Bellevue scores, controlled sampling differences related to age by using a "forced sample" of 1,072 prison inmates whose ages ranged from 15 to 75 years. Berkowitz (1) reported on Wechsler-Bellevue scores of 1,233 veterans ranging in age from 20 to 84 years. All three of these studies indicate that many intellectual functions do not decline with age and that such abilities as information and word knowledge even show continuous improvement well into the later adult years.

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THE SAMPLE AND TESTS

The data we are offering here are relevant to some of these questions which are raised by Shock and other investigators. We are comparing retest scores earned approximately 12 years apart by a group of intellectually superior adults on a highly difficult test. The subjects in this investigation are from the Stanford Study of the Gifted, a research program which was undertaken by L. M. Terman of Stanford University more than 30 years ago. In 1921-1922 a group of 1,528 intellectually gifted children ranging in age from 3 to 19 years (average 11.5 years) was selected by means of intelligence tests. The younger subjects, who were chiefly in elementary school and comprised about two-thirds of the total group, were located by the 1916 Stanford-Binet test. Their IQs ranged from 140 to 200 with a mean IQ of 151. A group of high school students who earned scores within the top 1 per cent for their age norms on the Terman Group Test comprised most of the older members of the sample (6). These gifted subjects have been followed continuously since 1921 to the present time by means of field worker interviews, questionnaires, tests, and personal correspondence. Information is available on the later careers of 98 per cent of the 1,434 members of the original group who were still living in 1950.

When in 1939 Terman planned to test

these people as adults, there was no test available which could be administered in a brief period and which had sufficient top to differentiate at a very high level. He found it necessary, therefore, to devise a new test. This test, called Concept Mastery, Form A, is composed of two subtests: I. Synonyms and Antonyms and II. Analogies. The test is given with no time limit, but ordinarily takes about 40 minutes to complete. Terman and Oden characterize the test as follows:

> "Both the synonym-antonym test and the analogies test are of the type commonly designated as 'verbal.' They are not as exclusively linguistic, however, as they appear to be. It is possible to devise verbal tests which measure not only vocabulary but a wide variety of information. In the selection of items, an effort was made to tap as many fields as possible by the use of concepts related to physical and biological science, medicine, mathematics, geography, history, logic, literature, psychology, art, religion, music, sports, *et cetera*. It was relatively easy to secure variety of this kind in the analogy items, but more difficult in the synonym-antonym items. The test has been named the Concept Mastery test because it deals chiefly with abstract ideas. Abstractions are the shorthand of the higher thought processes, and a subject's ability to function at the upper intellectual levels is determined largely by the number and variety of concepts at his command and on his ability to see relationships between them." (6).

Terman and Oden (6) have estimated, by comparison with a college sample who were given both the Stanford Binet and the Concept Mastery-A tests, that in the 1939-1940 testing the gifted subjects earned scores that average 2.5 standard deviations above the general population. This regression of about one-half a standard deviation from the original testing is in line with statistical expectations. The younger subjects scored lowest on the Concept Mastery. This fact was attributed to their youth at the time of selection and the consequent greater likelihood of regressive changes in relative scores during growth.

For use in the most recent testing of these subjects, in 1950-1952, Terman and Oden devised an alternate form of the Concept Mastery. Tests of reliability and validity of Form B show it to be as good as, and probably superior in many ways, to Form A.

In order to secure equivalent scores for Forms A and B we have given both forms, either in immediate succession or at one-week intervals, to 148 college undergraduates and other adults. Form A was given first to half of the subjects and Form B first to the other half. This sample was composed of 108 Stanford undergraduates and 40 graduate students and faculty members at the University of California. After correction for practice effects, the transformation by "line of equivalents" was made and a conversion table of Form B to B(E) scores was set up. For this sample of 148 the r between the two forms is .94.

There were 954 gifted subjects who took Form A of the Concept Mastery Test in 1939-1940 and 1,004 who took Form B in 1950-1952, and of these 768 took both Form A and Form B. Their average age at the earlier testing was 29.5 years, with an S.D. of 3.7 years; at the later testing they averaged approximately 41.5 years. We have additional data on the husbands and wives of these subjects: 527 spouses took the test in 1939-1940 and 677 spouses took it in 1950-1952. Of these, 335 took both forms. The average age of the spouses in 1950-1952 is 41.2 years, S.D., 3.3 years. Their test scores in 1939-1940 averaged the same as a group of college graduates who took the test: that is, about 1.6 S.D. above the average for the general population. Our report is thus based on scores made by 1,103 twice-tested adults who are, with few exceptions, above average in intelligence.

In this paper all of the test-retest comparisons are between the 1939-1940 scores on Form A and 1950-1952 scores for the same individuals (unless otherwise indicated) on Form B(E). Some of these comparisons are made for both the subjects of the study and their spouses; other comparisons have been limited to the original gifted group, for whom we have more complete information.

Results

The test-retest correlations for the 12-year interval are generally high. The r is .88 for

422 gifted study men, and also .88 for 346 gifted study women; it is .92 for 144 husbands, and also .92 for 191 wives. Such difference as there is between the correlations for the gifted study subjects and their spouses can be accounted for by the greater variability in scores of the spouses who comprise a sample that is less highly selected in this respect.

The distributions of scores earned by the gifted men and women for the two testings are shown in figure 1, and the means and S.D.s are given in table 1. The scores at the later testing, when the subjects are approximately 12 years older, are consistently higher than for the first testing. The increases in scores amount to about half an S.D. and are highly significant, the level of confidence being better than .001 for both the men and the women.

Comparison with those who were tested only once indicates that the twice-tested groups are typical of the total sample. The mean score on Form A for the 422 gifted study men in the twice-tested sample is 98.65 and for the 95 who took only Form A the mean is 98.18. The Form B(E) scores are 114.90 for the twice-tested, and 116.98 for those who took only Form B. Similarly, for the women, the mean A score for the twice-tested sample of 346 is 94.88, and for those who took only Form A it is 89.98. The B(E)

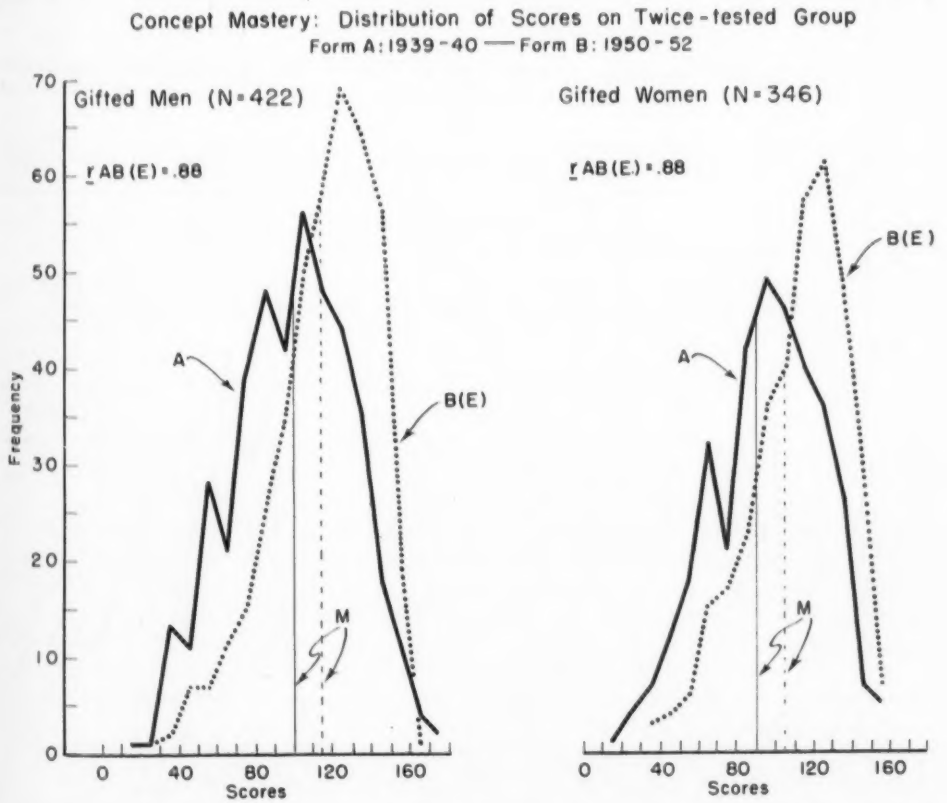

FIG. 1. Frequency distributions of Form A and Form B (E) Scores on the Concept Mastery Test: Gifted Study Men and Women.

scores average 110.45 and 105.42, respectively. The greatest difference is 5 points, or about one-sixth of the S.D. of any one group. Whatever is operating to produce higher scores at the later testing seems to be generally effective, and the failure of subjects to take the tests twice seems to have been unrelated to their ability.

The scores for the twice-tested spouses are also given in table 1, and their distributions are shown in figure 2. The increases are not quite so great, but they are there, and significant at better than the .001 level of confidence.

When other investigators have made comparisons of age changes in scores on synonym-antonym and analogies tests they have found a greater difference between the two types of function at the older ages. This difference usually takes the form of a greater decrement with age in the analogies scores. Jones and Conrad (3), for example, using the Army Alpha test, found that the analogies scores drop off more rapidly with age. Owens' (4) twice-tested college men improved .145 S.D. on the analogies subtest and .549 S.D. on the synonym-antonym test. We should expect, therefore, that the synonym-antonym scores earned by our subjects will increase more than the analogies. This information is also given in table 1. All increments, in both subtests, are highly significant for all 4 groups of subjects. Although the synonym-antonym scores increase on the average about half an S.D., the analogies scores improve by about one-third an S.D. This latter is more

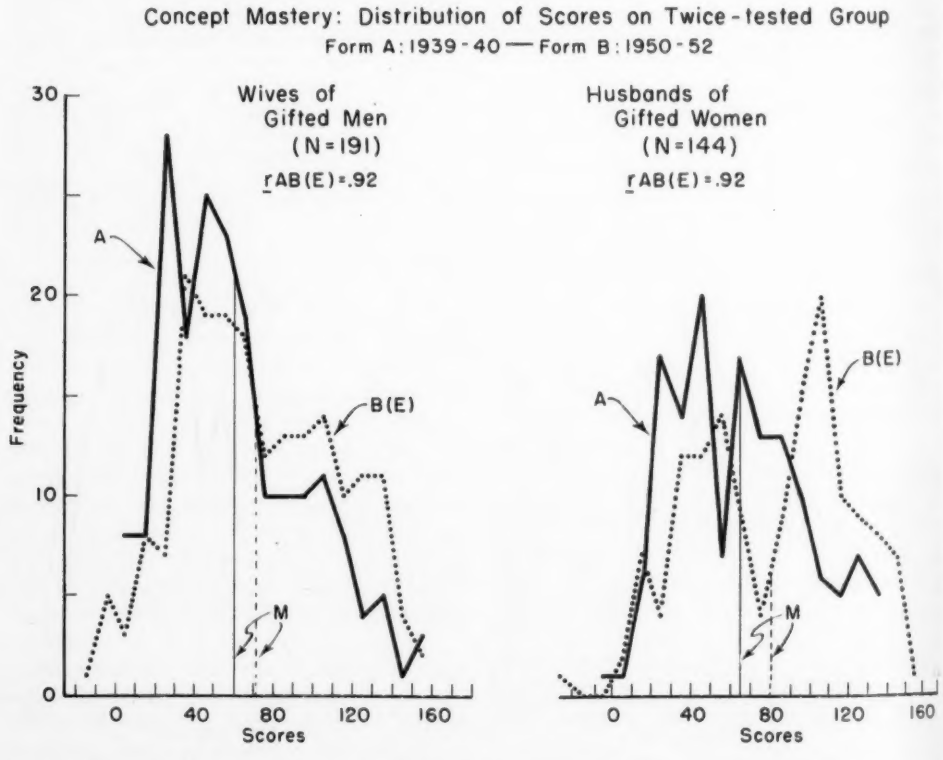

FIG. 2. Frequency distributions of Form A and Form B (E) scores on the Concept Mastery Test: Husbands and Wives of Gifted Study subjects.

TABLE 1. MEANS, STANDARD DEVIATIONS, AND TEST-RETEST COMPARISONS OF SCORES ON THE CONCEPT MASTERY TEST.

	Form A			Form B(E)			Difference B(E)-A*
	N	Mean	S.D.	N	Mean	S.D.	
Total Test							
Twice-tested							
Gifted study men	422	98.6	30.8	422	114.9	26.2	16.3
Gifted study women	346	94.9	28.5	346	110.4	25.3	15.5
Husbands	143	65.3	34.5	143	80.2	39.0	14.9
Wives	191	59.8	35.1	191	71.2	39.2	11.4
Tested Once Only†							
Gifted study men	95	98.2	33.8	129	117.0	30.0	18.8
Gifted study women	73	90.0	27.6	98	105.4	26.7	15.4
Synonym-Antonym Subtest							
Twice-tested							
Gifted study men	422	55.7	22.5	422	68.3	19.9	12.6
Gifted study women	346	55.2	20.1	346	66.8	18.6	11.6
Husbands	143	33.1	24.2	143	44.6	27.0	11.5
Wives	191	31.1	24.2	191	40.8	26.7	9.7
Analogies Subtest							
Gifted study men	422	43.3	9.9	422	47.1	8.4	3.8
Gifted study women	346	40.1	10.2	346	44.4	8.9	4.3
Husbands	143	31.9	12.2	143	35.8	13.4	3.9
Wives	191	28.5	12.2	191	30.5	14.3	2.0

* All differences are significant above the .001 level of confidence.

† 10 men and 8 women not included here died in the interval between 1940 and 1951.

than twice the increment that Owens found for an interval two and a half times as long in the Army Alpha analogies. Although they are called by the same name, the two tests may not be closely similar. Possibly the content of the analogies test used here is heavily weighted with the same kind of verbal knowledge that is measured in the synonym-antonym.

In general, we may conclude that the trend toward increase in retest scores is a function of the entire Concept Mastery test. The average gains are a little larger for the synonym-antonym, and for the groups who originally tested higher. Nevertheless, the gains are highly significant for both sexes and for both gifted subjects and spouses. It may be noted here, also, that for the gifted study subjects the S.D.s are consistently smaller at the second testing, while the reverse is true for the spouses.

With the fact established that the scores of these adults increase on their retests, we turn now to an attempt to discover factors that may be related to the change. Of course not all of the people gained in scores. A few, only about 9 per cent, actually lost more than 5 points: in one or two instances the loss was

as great as 25 to 30 points, or about 1 S.D. of the population here studied. Large gains, however, were frequent. There are 97 instances (9 per cent) of gains of 35 points or more, and there is one gain of 62 points, or about 2 S.D.s. This would be the equivalent of about 27 IQ points (6).

It has seemed reasonable to expect that the change in score, the tendency to gain or to lose in ability during these adult years, could be due to the nature of the persons' activities as reflected in such things as occupational level or amount of education. Or the changes could be related to general health or emotional adjustment, or to changes in motivation in taking the test itself. Or it could be related to age; perhaps the losses were more frequent among the older subjects. There is the further possibility that changes are a function of the initial score, either regression from extremes, or a tendency for greater gains to occur at certain levels of ability.

To take up first the matter of relation to *initial score*: the scattergrams of change in score in relation to initial score are shown in figures 3 to 6. When we eliminate the 3 men who were nearest the ceiling on Form A and who, in the equating of the two forms, were forced to lose a few points on the retest Form B(E), there remains some evidence of regression in the scores of both the men and the women in the gifted study. However, among the spouses regression is less evident, and a fair number of low-scoring spouses do not regress upward toward the mean but score even lower on the second test. Also, with few exceptions, gains of 35 points or more occur among those whose Form A scores range between 35 and 100, and tend not to be at the lowest extreme of the scale. At the upper extreme large gains are impossible, and a

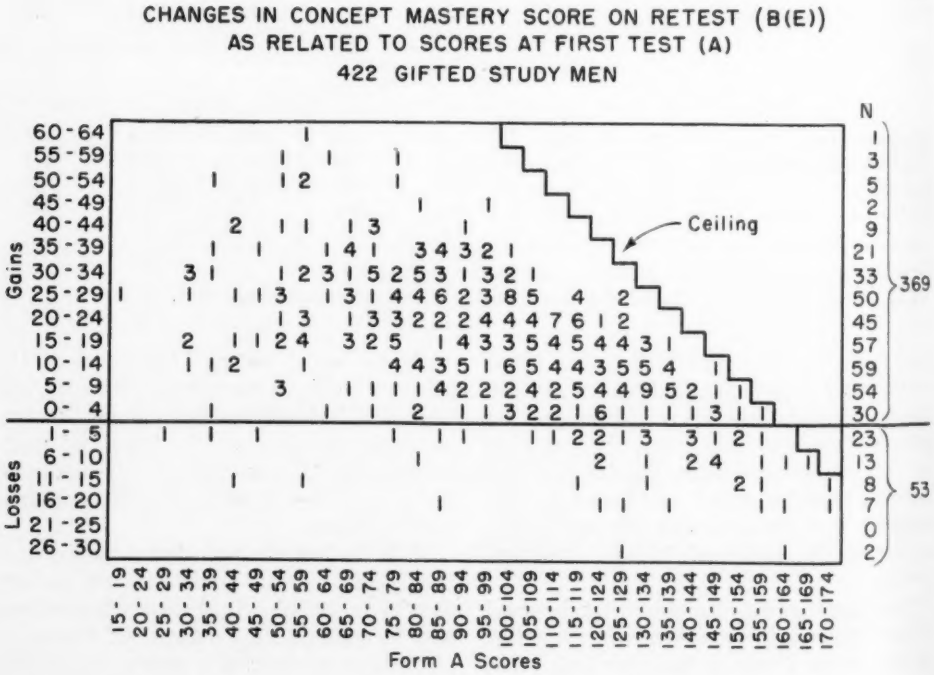

FIG. 3. Changes in Concept Mastery score on retest (Form B (E)) as related to scores at first test (Form A), for Gifted Study men.

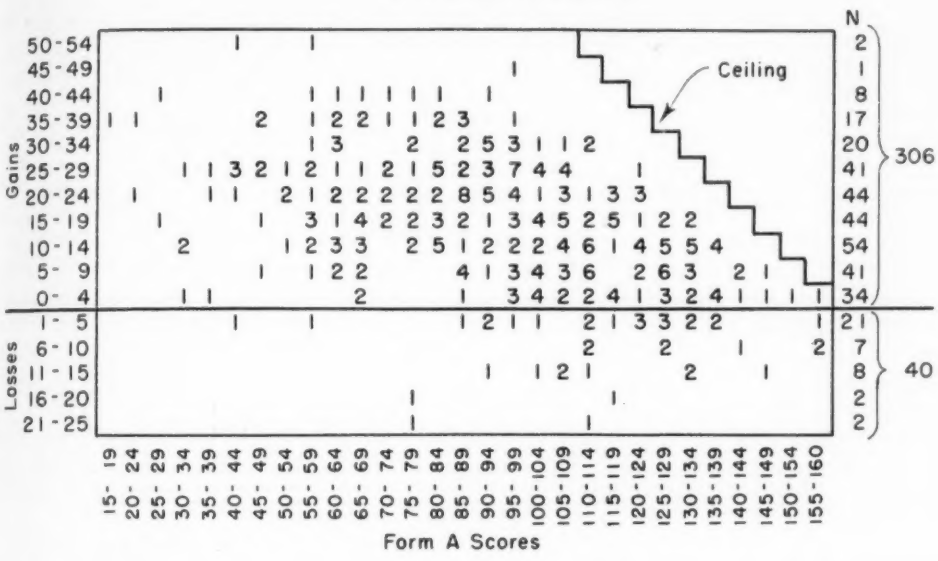

FIG. 4. Changes in Concept Mastery score on retest (Form B (E)) as related to scores at first test (Form A), for Gifted Study women.

few high scorers crowd the ceiling of the test. This ceiling, whether it is in the test itself, or at the real upper limit of the subjects' ability, serves to reduce the variability of retest scores in the high-scoring groups. Regression, it seems, accounts for only a part of the changes in scores from the first to the second test.

Although there was general high motivation among the people taking the tests, there were probably some whose motivation changed on the retest. We have no way of identifying these individuals. Such changes could very well occur, perhaps for different reasons, at all levels of ability.

The relationships between Concept Mastery score and Occupational Classification of the gifted subjects are given in tables 2 and 3. The classifications are according to occupations at the time of testing; therefore, the composition of an occupational group at the two testings is not identical and will represent some shifts in occupation as well as individual changes in score. Furthermore, the figures for Form A are for the total number tested, while Form B(E) data are limited to the twice-tested subjects.

At the first testing occupational classification in the case of men was definitely related to Concept Mastery score, but at the second testing, although there is still a relation between scores and occupational class, the differences between classes are greatly reduced. The lower the occupational group, the greater the gain in scores. The reduction in class differences is reflected in the critical ratios. For example, the CR between mean scores of the men in Group I compared with Groups III, IV, V, and VI combined is 9.5 on Form A and 5.8 on Form B(E). Of course, the higher scores earned in occupational group I are so much nearer the test ceiling that for many of these men there was no possibility of large gains.

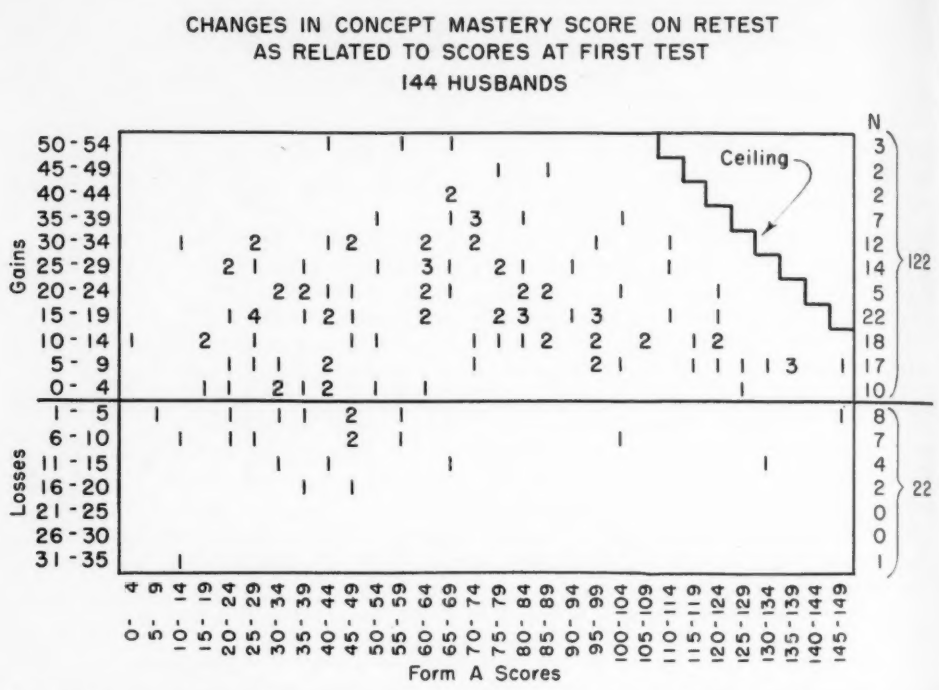

FIG. 5. Changes in Concept Mastery scores on retest (Form B (E)) as related to scores at first test (Form A), for husbands of Gifted Study women.

The women in this study for the most part have not been interested in careers, which may explain why their occupational classifications show less differentiation on the basis of Concept Mastery. The largest class, housewives who are not gainfully employed, seems to be representative of the total group. At the first testing no occupational class earned scores significantly different from any other class. At the later testing, however, the women in the "other professions" group forged ahead to earn the highest average score. The B(E) scores of this group are significantly higher than those earned by the housewives and by those in office and business occupations, the two lowest-scoring classes. The women in college teaching and research, who in 1940 tested highest, made practically no gain, while the other 4 groups gained approximately equal amounts.

Some interesting things come out of the comparison of A and B(E) scores of professional men when they are grouped according to type of profession, as shown in table 4. In 1939-1940 the engineers made the lowest scores, and these were significantly below scores made by university teachers. In 1950-1952 the engineers have made large gains, and are at the average of the total professional group. Their place as lowest scorers has been taken by those who teach below the university level. The difference between the two groups of teachers is significant at the .03 level of confidence at the first testing and at the .05 level at the second test.

In general the tendency has been for the scores of all occupational groups to improve, the lower-scoring ones most, so that here again we find smaller differences between groups than were present in 1940. This trend, too, may be attributed in part to ceilings on B(E) scores limiting the gains of those who originally scored very high.

The *educational level* achieved by subjects

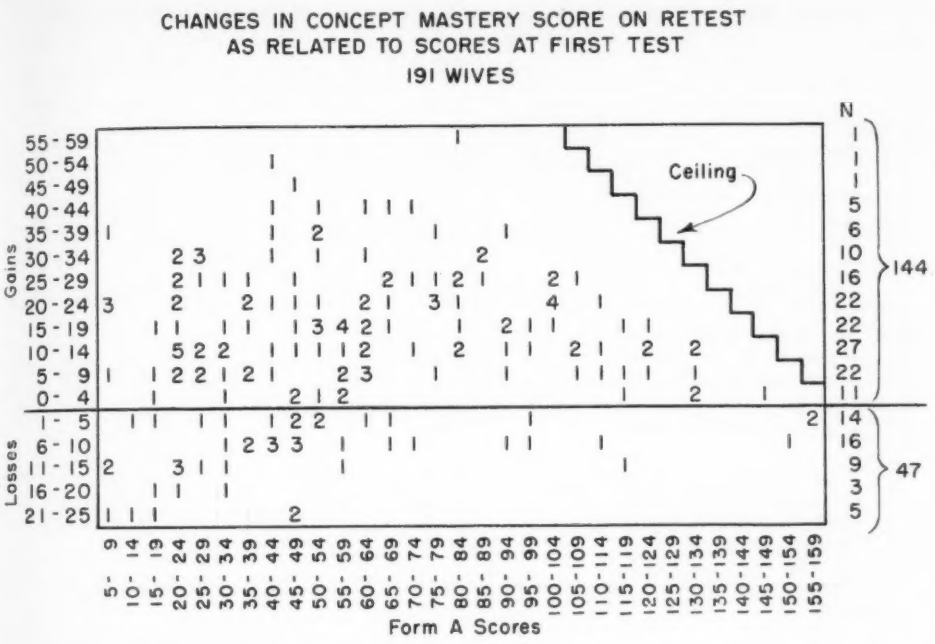

FIG. 6. Changes in Concept Mastery scores on retest (Form B (E)) as related to scores at first test (Form A), for wives of Gifted Study men.

of the gifted study correlates positively with their intelligence test scores. In this respect our data are in agreement with the usual findings. The data on education are given in tables 5, 6, 7, and 8. In order to maintain a constant sample, we have grouped subjects according to their education in 1950-1952. Only a few who had not quite completed their schooling in 1939-1940 would have been classified differently at that time. The gains in score occur in all educational levels, but seem to be somewhat greater for those with less education. This tendency is more evident for the men than for the women. To the extent that it occurs, it is in accord with the general tendency already noted for those groups scoring low at the first testing to gain most on the retest. It is contrary, in this instance, to Owens' finding of greater gains in Army Alpha and particularly, the analogies subtest, among his subjects with over five years of college (4). Differences in method of selecting the samples may account for this discrepancy.

Mental health and general adjustment were rated on a three-point scale by Terman and Oden on the 1940 data (6) from all available information about each subject of the gifted group. Using the same method and criteria, the ratings were made again on the 1952 data. Most subjects are classed as normal or as having "satisfactory adjustment." Category III includes only those with serious maladjustment, in some instances including a history of hospitalization. The relations of these ratings to Concept Mastery scores are shown in table 9 for the subjects of the gifted study. In this comparison the data for Form A are as published in Volume IV (6), while the data for Form B(E) are for the twice-tested sample.

There is, for both sexes, a tendency for the more seriously maladjusted individuals to earn higher scores. The differences are great-

TABLE 2. CONCEPT MASTERY SCORES BY OCCUPATIONAL CLASSIFICATION FOR GIFTED MEN.

	Form A*			Form B(E)*		
	N	Mean	S.D.	N	Mean	S.D.
I. Professional	215	110.4	27.0	187	123.3	21.8
II. Semi-professional and higher business	114	96.3	32.7	157	110.4	26.1
III. Clerical, retail business, skilled trades	107	82.6	26.4	59	100.1	29.2
IV.-VI. Agricultural, minor clerical, minor business, semi-skilled, or slightly skilled occupations	44	82.7	31.6	12	108.7	26.9
Differences between means:		CR	P		CR	P
Group I vs. II		3.9	<.001		4.9	.001
Group I vs. III-VI		9.5	<.001		5.8	.001
Group I vs. IV-VI		5.4	<.001		1.8	.07
Group II vs. III-VI		3.6	<.001		2.2	.03

* The Form A data are for all cases tested (6, p. 183) and the Form B(E) figures are for the twice-tested subjects only.

TABLE 3. CONCEPT MASTERY SCORES BY OCCUPATION FOR GIFTED WOMEN.

	Form A*			Form B(E)*		
Occupation	N	Mean	S.D.	N	Mean	S.D.
1. College teaching; higher professions†	16	116.4	15.1	13	118.3	25.0
2. Teaching below college level	50	97.9	24.8	26	115.3	25.7
3. Other professions	50	104.3	27.8	48	121.2	17.2
4. Office and business	77	91.1	28.5	56	104.9	25.6
5. Housewife (not employed)	176	91.8	27.3	203	108.6	25.8
Difference between means:					CR	P
1 vs. 4	No significant differences Form A				1.74	.08
2 vs. 4					1.71	.09
3 vs. 4					3.86	<.001
3 vs. 5					4.09	<.001

* The Form A data are for all cases tested (6, p. 183) and the Form B(E) figures are for the twice-tested subjects only.

† Requiring a Ph.D., M.D., or LLB. degree.

er for the men and for the 1940 data. Those whose adjustment was classified as satisfactory made greater gains, and again the differences between classes are reduced at the later testing. However, large gains in scores occur in all three classes.

Self-ratings of physical health were not significantly related to the Concept Mastery

TABLE 4. COMPARISON OF CONCEPT MASTERY SCORES OF MEN IN OCCUPATIONAL CLASS I ACCORDING TO PROFESSION.

Profession*	Form A			Form B(E)			
	N	Mean	S.D.	N	Mean	S.D.	Difference B(E)-A
1. University teacher or researcher	21	128.2	25.1	16	132.1	18.1	3.9
2. Teacher below university level	30	110.8	32.8	24	117.8	28.2	7.0
3. Authors and Journalists	14	113.6	30.7	8	127.8	.....	14.2
4. Lawyers	57	111.5	23.4	51	123.4	18.8	11.9†
5. Physicians	23	112.5	26.0	21	120.2	19.9	7.7
6. Chemists	20	110.0	21.1	17	123.9	13.5	13.9‡
7. Engineers	32	102.2	23.6	30	122.8	23.0	20.6†
7a. Twice-tested Engineers so-classed both times	22	103.7	24.1	22	121.4	24.5	17.7‡
Differences between means:		CR	P		CR	P	
1 vs. 2		2.13	.03		1.95	.05	
1 vs. 5		2.03	.04		1.90	.06	
1 vs. 7		3.77	$<.001$		1.51	.13	

* A group of miscellaneous professions is omitted.
† Significant at the .01 level of confidence or better.
‡ Significant at the .02 level of confidence.

TABLE 5. CONCEPT MASTERY SCORES BY AMOUNT OF EDUCATION FOR GIFTED MEN.

Education	N	Form A		Form B(E)	
		Mean	S.D.	Mean	S.D.
1. Ph.D. degree	25	127.3	22.9	138.5	14.1
2. M.D. degree	21	111.2	24.0	120.2	19.9
3. LLB. degree	51	109.6	23.4	124.5	18.5
4. Other graduate degrees	54	109.5	30.5	121.4	23.9
5. 1 or more years graduate work; no graduate degree	35	107.9	30.4	122.5	25.5
6. Bachelor's degree	104	96.1	27.6	113.2	25.5
7. 1 to 4 years college; no degree	75	82.4	28.4	104.5	26.4
8. High school and technical or business training	25	82.5	27.1	102.9	25.6
9. High school graduation or equivalent	32	81.1	30.6	98.2	27.7
Difference between means:		CR		CR	
1 vs. 9*		5.37		7.12	
1 vs. 6*		5.87		6.72	

* Significant above the .001 level of confidence.

TABLE 6. CONCEPT MASTERY SCORES BY AMOUNT OF EDUCATION FOR GIFTED WOMEN.

Education	N	Form A		Form B(E)	
		Mean	S.D.	Mean	S.D.
1. Ph.D., M.D., LLB. degrees	11	119.0	13.7	123.6	16.2
2. Other graduate degrees	59	105.9	24.0	120.6	19.8
3. 1 or more years graduate study, no graduate degree	60	103.7	27.2	117.3	25.0
4. Bachelor's degree	96	95.8	23.1	112.6	21.6
5. 1 to 4 years college; no degree	58	86.2	30.7	103.3	28.8
6. High school and technical or business training	13	89.1	24.7	101.4	19.4
7. High school graduation or equivalent	49	75.5	30.6	95.5	26.0
Differences between means:		CR		CR	
1 vs. 6*		7.23		4.57	

* Significant above the .001 level of confidence.

TABLE 7. SUB-SCORES ON CONCEPT MASTERY BY AMOUNT OF EDUCATION FOR GIFTED MEN.

Education	N	Synonym-Antonym				Analogies			
		Form A		Form B(E)		Form A		Form B(E)	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
1. Ph.D. degree	25	76.5	17.0	83.7	11.6	52.6	6.8	55.0	4.5
2. M.D. degree	21	62.6	18.2	71.6	16.1	49.6	7.3	48.9	6.3
3. LLB. degree	51	66.1	16.6	77.0	12.5	43.8	7.4	48.4	6.9
4. Other graduate degrees	54	62.5	21.8	72.3	18.2	47.7	9.2	49.9	7.6
5. 1 or more years graduate study; no graduate degree	35	61.6	24.1	72.8	19.0	46.1	8.7	50.9	8.3
6. Bachelor's degree	104	53.0	21.1	66.8	20.7	43.1	8.7	46.7	7.5
7. 1 to 4 years college; no degree	75	43.7	20.4	61.3	20.1	38.7	9.8	44.1	8.6
8. High school and technical or business training	25	47.3	19.9	58.1	20.2	36.6	9.2	43.4	6.1
9. High school graduation or equivalent	32	44.2	21.7	47.3	19.7	37.2	6.8	40.3	9.4
Differences between means:		CR	P	CR	P	CR	P	CR	P
1 vs. 9		6.30	<.001	8.68	<.001	7.38	<.001	5.84	<.001
1 vs. 6		5.93	<.001	5.49	<.001	7.38	<.001	6.10	<.001

scores at either testing, and so are obviously not significant determiners in the intellectual functioning of these adults.

In the light of earlier findings, that intelligence test scores of adults decrease with age, perhaps age is the crucial factor to be considered here. The one thing that these 1,103 people have in common is that between the two testings they grew about twelve years older. Because the year of birth of the gifted subjects ranged from 1903 to 1920, it has been possible to subdivide the samples into several age groups. We can thus study the trends of scores for groups ranging from

TABLE 8. SUB-SCORES ON CONCEPT MASTERY BY AMOUNT OF EDUCATION FOR GIFTED WOMEN.

Education	N	Synonym-Antonym				Analogies			
		Form A		Form B(E)		Form A		Form B(E)	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
1. Ph.D., M.D., LLB. degrees	11	68.1	13.0	77.2	9.6	49.7	5.4	49.3	7.2
2. Other graduate degrees	59	62.0	17.4	72.3	16.2	44.5	8.2	48.3	6.6
3. 1 or more years graduate study; no graduate degree	60	59.3	19.8	69.2	19.4	44.8	9.6	48.3	8.3
4. Bachelor's degree	96	56.4	17.2	68.3	16.2	40.3	8.3	45.6	6.9
5. 1 to 4 years college; no degree	58	48.8	22.2	62.8	20.4	36.7	9.7	40.9	9.8
6. High school and technical or business training	13	49.9	20.2	62.2	14.8	37.4	5.0	39.7	6.1
7. High school graduation or equivalent	49	44.9	21.0	58.0	20.6	30.9	11.2	37.0	8.4
Differences between means:		CR	P	CR	P	CR	P	CR	P
1 vs. 7		4.71	$<.001$	4.67	$<.001$	8.29	$<.001$	4.96	$<.001$

TABLE 9. CONCEPT MASTERY SCORES COMPARED FOR GENERAL ADJUSTMENT AND MENTAL HEALTH.

Gifted Men

Rating of Adjustment	Form A Scores*			Form B(E) Scores*		
	N	Mean	S.D.	N	Mean	S.D.
1. Satisfactory	407	95.2	30.9	296	112.0	26.5
2. Some maladjustment	91	108.0	31.2	94	120.6	24.0
3. Serious maladjustment	18	119.5	23.6	28	129.1	20.6
Differences between means:		CR	P		CR	P
1 vs. 2+3		4.48	$<.001$		4.00	$<.001$

Gifted Women

1. Satisfactory	344	92.4	28.7	238	108.6	25.6
2. Some maladjustment	59	98.6	25.4	88	115.4	22.1
3. Serious maladjustment	17	108.6	22.1	22	115.4	29.5
Differences between means:		CR	P		CR	P
1 vs. 2+3		2.45	.01		2.43	.015

* The N's for Form A are for the total group tested; the B(E) scores are for the twice tested group only.

their early twenties at the first test, to their late forties at the second test. These data are given in tables 10 and 11 for the gifted subjects, and are shown graphically in figures 7 and 8. There are 4 age-groups of gifted study men, and 3 age-groups of gifted study women. Figure 7 also includes 4 age-groups each of the husbands and the wives.

TABLE 10. CONCEPT MASTERY SCORES FOR AGE AT TESTING GIFTED MEN.

Year of Birth	1915 or later		1910–1914		1905–1909		Before 1905	
Form of Test	A	B(E)	A	B(E)	A	B(E)	A	B(E)
Age at testing (Mean) Years	23	35	27	39	32	44	36	48
N	34		208		144		36	
Total Test								
Mean	86.5	106.5	98.1	114.6	105.7	119.8	90.8	105.1
S.D.	36.8	33.2	31.5	26.0	28.0	22.9	23.4	22.2
Synonym-Antonym								
Mean	46.8	61.4	54.7	67.5	60.7	72.6	49.5	62.3
S.D.	27.6	24.7	22.3	20.8	21.3	17.1	18.0	16.7
Analogies								
Mean	38.6	45.1	42.8	47.2	45.5	48.2	41.7	44.1
S.D.	11.2	9.6	10.5	8.4	8.8	7.8	7.2	8.3
Differences: B(E)-A P.	.02		$<.001$		$<.001$		.01	

TABLE 11. CONCEPT MASTERY SCORES FOR AGE AT TESTING GIFTED WOMEN.

Year of Birth	1915 or later		1910–1914		Before 1910	
Form of Test	A	B(E)	A	B(E)	A	B(E)
Age at Testing Approximate	23	35	27	39	33	45
N	35		191		120	
Total Test						
Mean	74.4	94.5	94.6	110.5	102.7	116.3
S.D.	33.8	31.9	27.9	24.4	25.0	22.9
Synonym-Antonym						
Mean	39.6	54.8	55.0	66.8	59.8	70.2
S.D.	20.3	21.7	20.1	18.7	17.9	16.0
Analogies						
Mean	35.9	39.7	39.2	44.3	42.6	46.0
S.D.	13.2	12.2	9.9	8.1	9.2	8.4
Differences: B(E)-A P.	.004		$<.001$		$<.001$	

In the figures, for each group the mean scores at first and second testing are connected by a line. The impressive thing that comes out of this division into age groups is that all groups show similar and significant tendencies to increase in scores over the twelve-year interval. There is, perhaps, a slight tendency for the increments to become smaller with successively older age-groups. This tendency is more evident for the analo-

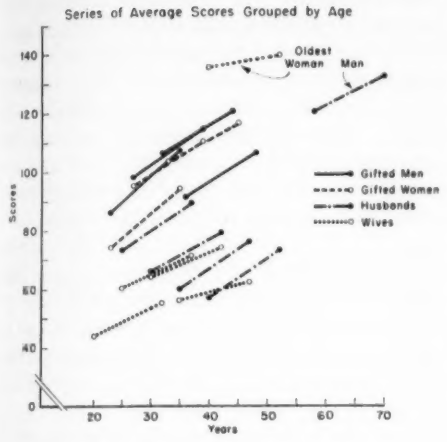

FIG. 7. Mean scores on the Concept Mastery test, subjects grouped according to age at the first testing. First and second tests for each group are connected.

gies than for the synonym-antonym subtest.

Although there seem to be sampling differences in the abilities of the different groups, it also becomes evident that the lower scores of the younger subjects are in part a function of their age at the time of testing. This is true, in particular, for the young gifted men, who at the second testing did as well as the older men did at the same age. The younger women and the older men in the gifted groups seem, at these testings, to be in general somewhat less able than the rest of the gifted subjects. However, it should be noted that these groups are composed of comparatively few cases.

The age-groups of the spouses show greater variability. This may be accounted for by the facts that they were not selected for intelligence test scores in the first place and that the number in any one age-group is

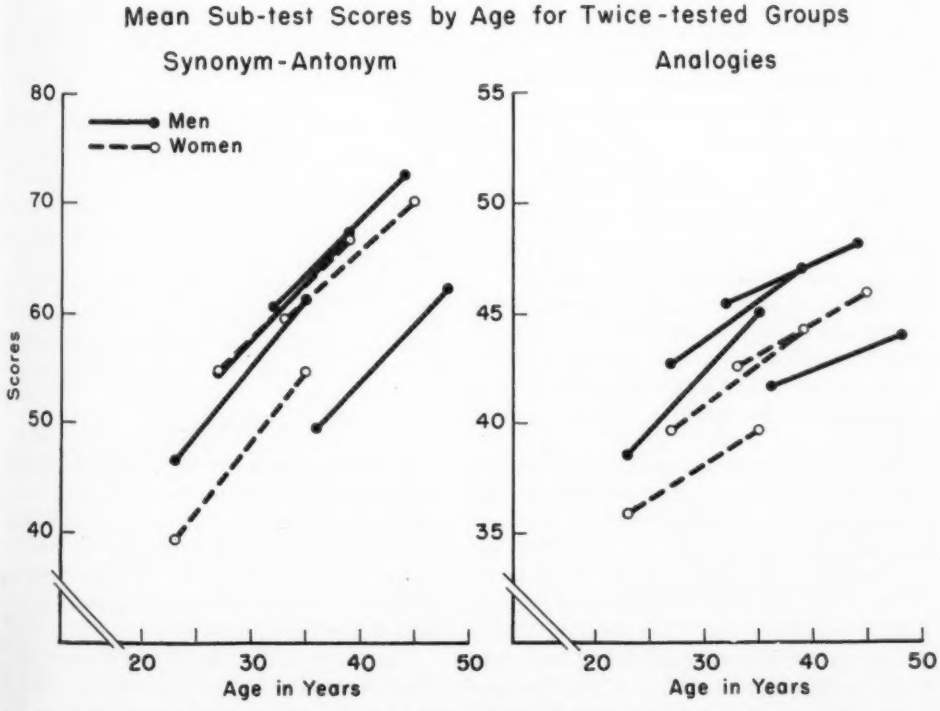

FIG. 8. Mean scores, by age groups, on the Concept Mastery sub-tests for Gifted Study subjects.

often very small. The spouses' highest scores seem to occur in the early and middle age ranges for the men and in the middle ranges for the women. But for any one age group there is the same tendency for scores to improve from the first to the second testing.

The spouses give us a few cases at more advanced ages than are available among the gifted subjects. The oldest is a man who was 70 at his second testing. His scores are indicated on figure 7, as are also those of the oldest woman, who was 52 at her second test. Both of these older people make superior scores, and both do better at the later testing than at the earlier.

Discussion

The material presented here is in disagreement with many of the results of earlier studies of intelligence in adults. The apparent disagreements, however, may be due to the fact that much of this material is of a kind that has not been secured before. Our subjects are well-motivated and highly intelligent. The test used was designed to differentiate abilities at the upper levels. Finally, the tests have been repeated on the same subjects after an interval of time that is long enough to allow for significant changes to take place. Our material does not, however, cover the later ages at which real senescent decrements in intellectual functioning are to be expected. Furthermore, our material is not concerned with measures of speed, either in physical action or intellectual processes. The Concept Mastery test, rather, calls for knowledge of symbols and abstractions, and the ability to use these in relation to each other.

The implications to be drawn from our data are that this kind of knowledge and ability improves in superior adults, at least between the ages of 20 and 50. This improvement occurs about equally for all levels of education. It occurs in all levels of occupation represented, but to a greater extent among the middle occupational classes than in the higher classes. Also, within the professional class, the engineers and chemists, whose training was relatively specific and narrow, evidently broaden their abilities with time, so that on this general type of verbal test their scores attain equality with those of the other professions. This broadening tendency may operate generally among intelligent adults in our culture. Such a factor could serve to account for the reduction of class differences in scores at the second testing.

It should be noted that this leveling tendency occurs for subclasses within the groups of already high-scoring gifted study subjects. When we compare the 4 main groups the higher-scoring groups show the greater gains on the retest. The rank order, both of mean scores and of gains in scores is: gifted study men, gifted study women, husbands, and wives (table 1). The general tendency for greater increase in test scores to occur in the more highly intelligent persons is curtailed at the upper extremes of the test by a ceiling. It is impossible to say on the basis of these data whether these individuals would have gained in score on a test with more top, or whether they had already reached their upper limit.

The results of this study tend to be in agreement with those of Owens (4), who also retested the same subjects after a lapse of years. Thus the phenomenon of adult gains seems to be general and not a peculiarity of this test or this sample.

Intellectual changes after 50 should be investigated by similar means. It seems likely that there will be great individual differences in the age at onset of senescent decline.

Summary

A test designed to measure superior intelligence was administered twice, about twelve years apart, to 1,103 adults. Of these, 768 were selected as children, by Terman, for inclusion in the Stanford Study of Gifted Children. The other 335 are spouses of subjects in the Terman study.

There was a highly significant increase in scores at the second testing, both by the subjects of the gifted study and by their hus-

bands and wives. The order of mean scores, from highest to lowest, was the same as that of gains on the retests, i.e., gifted men, gifted women, husbands, and wives. The increases occurred in all occupational and educational levels represented, at all levels of ability tested, except where the test ceiling prevented, and at all ages from 20 to 50 years. The gains were found in both the synonym-antonym and the analogies halves of the test, but were somewhat larger in the former.

Variability of scores was less for the gifted study subjects and decreased at the second testing and with increasing age. Within these groups occupational, educational, and mental health class differences were reduced at the second testing. Variability of the spouses' scores was greater and increased on the retest.

The retests of this large group of superior adults give strong evidence that intelligence of the type tested by the Concept Mastery scale continues to increase at least through 50 years of age.

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BOOK REVIEWS

RORSCHACH RESPONSES IN OLD AGE, by Louise Bates Ames, Janet Learned, Ruth W. Metraux, and Richard N. Walker, Hoeber-Harper Publishers, New York, 1954, 229 pages, $6.75.

This book represents the second in a series of noteworthy developmental studies employing the Rorschach technique to come from the Gesell Institute of Child Development. Sampling the perceptual responses of children from 2 to 10 in their first book, the authors now switch with ease to the 3 decades of life from 70 to 100 with no restructuring of guiding developmental principles. Thus the present volume recognizes that the problems with which the field of gerontology should be concerned are no different from those encountered at any segment of the age curve—viz., growth, development, and maturation.

The major purposes of the volume, as stated by the authors, are to inquire whether or not patterned age changes in intellectual and emotional functions take place in the later decades of life and, if so, whether the Rorschach is a worthwhile tool for determining such changes. In this formulation of objectives, the authors seem, to this reviewer , to indulge in a kind of circularity which should be avoided in such studies. That is, in order to determine whether or not patterned changes occur in old age and in childhood, one must assume the validity of the chosen instrument for reflecting whatever changes exist. This assumption of validity then precludes use of the same data to reflect upon the usefulness of the test as a measure of such changes.

This same blending of objectives (or, more precisely, alternation of dependent and independent variables) is even more striking with respect to their break-down of cases into 3 groups designated as normal, presenile, and senile. No external criteria were employed for so classifying the subjects (which is not meant to imply that such criteria are easy to find), but rather quantitative and qualitative Rorschach findings were utilized as a basis of classification. Then statistical techniques were employed to determine whether or not the groups so differentiated managed to hold themselves apart with statistical reliability. The fact that they did so would hardly come as a surprise. The authors admit the circularity of this method of first differentiating the groups according to certain signs and then checking to see if the groups had different frequencies of the signs. However, they defend the procedure by pointing to the intragroup homogeneity which emerged in the total patterning of responses. While this sharpening of empiricism has certain merits, it also represents a kind of validity by fiat for the test which is insufficient to assure the clinician of the utility of the instrument in the gerontological field. Especially does this process make their later exposition of the Rorschach characteristics of the 3 groups a bit gratuitous, as the results are virtually predetermined.

This comment on methodology is one of the few criticisms of the present work which can be offered, for like the earlier volume by the same authors, *Child Rorschach Responses*, the work is meticulously executed, the many tables clear and informative, and the organization of material excellent. Subjects were 200 elderly individuals, one-third of whom lived in their own homes and the remaining two-thirds of whom were residents in private institutions. All were regarded as reasonably healthy, alert, and active. As would be expected, sampling was more adequate in the decades from 70 to 90, with only 13 cases older than 90. Sexes were not equally represented, as there were 140 women and only 60 men. The previously described breakdown of cases into three qualitative subgroups indicated that 140 of the subjects fell into the presenile group, with 41 being rated normal and 19 senile.

Reliance upon Rorschach test protocols for classifying the subjects is an indication that the authors did not find evidence of the clear-cut patterning of age changes which they had sought. In these 3 decades of life, the authors are forced to abandon their concept of "oldness" which has in the past represented the core of the Gesell developmental theory. Thus they find themselves unable to say the "70-year-old" with the same confidence with which they speak of the "7-year-old." This is interpreted as indicating that, with increasing maturity, individual differences in rate of growth cumulate so that by the time old age has been reach chronological age is no longer the most efficient predictor of the stage of the individual's development. This same point of view has been emphasized by other writers in relation to physiological age.

One finding which will perhaps disturb the advocate of the Rorschach technique as a research tool is the preponderance of qualitative signs relied upon to distinguish between the normal, presenile, and senile subjects. Furthermore, some of the most reliable signs relate to almost casual word usage by the subjects. When one considers that relatively little attention has been paid to such features in clinical studies with younger adults, one wonders if these signs are really as pathognomic of old age (especially senility) as they seem to be in the present study.

There is no question but that this volume marks a significant contribution to psychological research in gerontology. For several years now Rorschach studies have been accumulating in the literature as though the superstructure were ready to support them. Now at least the cornerstone has been laid, and further studies will no longer have to be cantilevered on slim shafts of subjectivity.

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STUDY OF OCCUPATIONAL RETIREMENT, A Preliminary Statistical Report on Health and Medical Examination Information, Department of Sociology and Anthropology, Cornell University, Ithaca, New York, 1954, 12 pages, mimeographed.

This is the second progress report of the Cornell longitudinal study of the effects of retirement. The present report covers results of a self-administered health questionnaire and medical examinations. Three thousand individuals are represented in the sample.

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Washington, D. C.

NEW YORK CITY'S SENIOR CITIZENS, Report of the Mayor's Advisory Committee for the Aged, New York, 1954, 3 volumes, mimeographed.

According to the most recent estimate, there are approximately 700,000 people 65 years of age and over, and several hundred thousand more between 60 and 65 years of age in this country's largest city. Increasing nine times as fast as the rest of New York City's population, the older people's needs were given explicit, comprehensive attention in October, 1949, with the establishment of the Mayor's Advisory Committee for the Aged.

This report is an account of the Committee's activities during the first four years of its existence. The immediate objectives of the Mayor's Committee have been the extension and improvement of adult education opportunities, community service, day center programs, employment, housing, legislation, medical care and research, nursing home standards, social service and counseling, and institutional care. All of these objectives are being pursued through subcommittees, and Volume I of the report comprises summary statements of their progress to date.

Underlying the work of the entire Committee is a Subcommittee on Research. In addition to its own progress report in Volume I, the findings of seven special research studies conducted by the subcommittee are presented in Volumes II and III. These constitute the longest part of the report, and fortunately, it is here that one finds the most interest and value as far as gerontologists everywhere are concerned.

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Rorschach Responses in Old Age, by Louis Bates Ames, Janey Learned, Ruth W. Metraux, and Richard N. Walker, Hoeber-Harper Publishers, New York, 1954, 229 pages, $6.75 (reviewed in this issue, page 108.

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JOURNAL OF GERONTOLOGY

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Section C

Organization Section and Index to Current Periodical Literature

INDEX TO CURRENT PERIODICAL LITERATURE

NATHAN W. SHOCK
Gerontology Section
National Heart Institute
National Institutes of Health

The subject categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given (*B.A.—Biological Abstracts; P.A.—Psychological Abstracts;* and *P.I.—Population Index*). Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the years 1900-1933*, 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Section, Baltimore City Hospitals, Baltimore, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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ORGAN SYSTEMS

I. Blood

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V. Endocrine System

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See also No. 12688.

VIII. Lymphatic System

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X. Nervous System

(neurology)

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XI. Reactions of the Body as a Whole

(allergy, anoxia, anesthesia, anthropometry, drugs, exercise, immunity, sleep, and temperature regulation)

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(ovaries, testes, see Endocrine System)

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